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(54) **Title:** METHODS FOR DIAGNOSING AND TREATING HEART DISEASE

(57) **Abstract:** The invention provides methods of diagnosing heart disease, such as heart failure, screening methods for identifying compounds that can be used to treat or to prevent heart disease, and methods of using these compounds to treat or to prevent heart disease. The invention also provides animal model systems for carrying out the screening methods.

METHODS FOR DIAGNOSING AND TREATING HEART DISEASE

Field of the Invention

5 This invention relates to methods for diagnosing and treating heart disease.

Background of the Invention

Heart disease is a general term used to describe many different heart conditions. For example, coronary artery disease, which is the most
10 common heart disease, is characterized by constriction or narrowing of the arteries supplying the heart with oxygen-rich blood, and can lead to myocardial infarction, which is the death of a portion of the heart muscle. Heart failure is a condition resulting from the inability of the heart to pump an adequate amount of blood through the body. Heart failure is not
15 a sudden, abrupt stop of heart activity, but, rather, typically develops slowly over many years, as the heart gradually loses its ability to pump blood efficiently. Risk factors for heart failure include coronary artery disease, hypertension, valvular heart disease, cardiomyopathy, disease of the heart muscle, obesity, diabetes, and a family history of heart failure.

20

Summary of the Invention

The invention provides diagnostic, drug screening, and therapeutic methods based on the observation that mutation of the *titin* gene leads to a phenotype in zebrafish that is similar to mammalian heart failure.

In one aspect, the invention provides a method of determining whether a test subject (*e.g.*, a mammal, such as a human) has, or is at risk of developing, a *titin*-related disease or condition (*e.g.*, heart failure). This method involves analyzing a nucleic acid molecule of a sample from the
5 test subject to determine whether the test subject has a mutation (for example, a mutation in a cardiac-specific exon, such as the N2B exon; *e.g.*, the *pickwick* mutation; see below) in a *titin* gene. The presence of such a mutation is an indication that the test subject has, or is at risk of developing, a *titin*-related disease. This method can further involve using
10 nucleic acid molecule primers specific for the *titin* gene for nucleic acid molecule amplification of the *titin* gene by the polymerase chain reaction, or sequencing *titin* nucleic acid molecules from the test subject.

In another aspect, the invention provides a screening method for identifying a compound that can be used to treat or to prevent heart failure.
15 This method involves contacting an organism (*e.g.*, a zebrafish) having a *titin* mutation (for example, a mutation in a cardiac-specific exon, such as the N2B exon; *e.g.*, the *pickwick* mutation) and a phenotype characteristic of heart failure with the compound, and determining the effect of the compound on the phenotype. Detection of an improvement in the
20 phenotype indicates the identification of a compound that can be used to treat or to prevent heart failure.

In another aspect, the invention provides a method of treating or preventing heart disease, such as heart failure, in a patient. This method involves administering to the patient a compound identified using the
25 screening method described above. A patient treated using this method can have a mutation in the *titin* gene.

In a further aspect, the invention provides a non-human animal (*e.g.*, a zebrafish or a mouse) that has a mutation in a *titin* gene. The

mutation can be, for example, in a cardiac-specific exon of the *titin* gene, such as the N2B exon, and can result in production of a truncated titin product, for example, by the introduction of a stop codon.

By “polypeptide” or “polypeptide fragment” is meant a chain of
5 two or more amino acids, regardless of any post-translational modification (e.g., glycosylation or phosphorylation), constituting all or part of a naturally or non-naturally occurring polypeptide. By “post-translational modification” is meant any change to a polypeptide or polypeptide fragment during or after synthesis. Post-translational modifications can be
10 produced naturally (such as during synthesis within a cell) or generated artificially (such as by recombinant or chemical means). A “protein” can be made up of one or more polypeptides.

By “titin,” “titin protein,” or “titin polypeptide” is meant a polypeptide that has at least 45%, preferably at least 60%, more preferably
15 at least 75%, and most preferably at least 90% amino acid sequence identity to the sequence of the human (see below) or the zebrafish titin polypeptides. Polypeptide products from splice variants of *titin* gene sequences and *titin* genes containing mutations are also included in this definition. A titin polypeptide as defined herein plays a role in heart
20 development, modeling, structure, and contractility. It can be used as a marker of heart disease, such as heart failure.

By a “*titin* nucleic acid molecule” is meant a nucleic acid molecule, such as a genomic DNA, cDNA, or RNA (e.g., mRNA) molecule, that encodes titin, a titin protein, a titin polypeptide, or a portion thereof, as
25 defined above.

The term “identity” is used herein to describe the relationship of the sequence of a particular nucleic acid molecule or polypeptide to the sequence of a reference molecule of the same type. For example, if a

polypeptide or nucleic acid molecule has the same amino acid or nucleotide residue at a given position, compared to a reference molecule to which it is aligned, there is said to be “identity” at that position. The level of sequence identity of a nucleic acid molecule or a polypeptide to a
5 reference molecule is typically measured using sequence analysis software with the default parameters specified therein, such as the introduction of gaps to achieve an optimal alignment (e.g., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705,
10 BLAST, or PILEUP/PRETTYBOX programs). These software programs match identical or similar sequences by assigning degrees of identity to various substitutions, deletions, or other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine, valine, isoleucine, and leucine; aspartic acid, glutamic
15 acid, asparagine, and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine.

A nucleic acid molecule or polypeptide is said to be “substantially identical” to a reference molecule if it exhibits, over its entire length, at least 51%, preferably at least 55%, 60%, or 65%, and most preferably
20 75%, 85%, 90%, or 95% identity to the sequence of the reference molecule. For polypeptides, the length of comparison sequences is at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably at least 35 amino acids. For nucleic acid molecules, the length of comparison sequences is at least 50
25 nucleotides, preferably at least 60 nucleotides, more preferably at least 75 nucleotides, and most preferably at least 110 nucleotides.

A *titin* nucleic acid molecule or titin polypeptide is “analyzed” or subject to “analysis” if a test procedure is carried out on it that allows the

determination of its biological activity or whether it is wild type or mutated. For example, one can analyze the *titin* genes of an animal (*e.g.*, a human or a zebrafish) by amplifying genomic DNA of the animal using the polymerase chain reaction, and then determining whether the amplified
5 DNA contains a mutation, for example, the *pickwick* mutation, by, *e.g.*, nucleotide sequence or restriction fragment analysis.

By “probe” or “primer” is meant a single-stranded DNA or RNA molecule of defined sequence that can base pair to a second DNA or RNA molecule that contains a complementary sequence (“target”). The stability
10 of the resulting hybrid depends upon the extent of the base pairing that occurs. This stability is affected by parameters such as the degree of complementarity between the probe and target molecule, and the degree of stringency of the hybridization conditions. The degree of hybridization stringency is affected by parameters such as the temperature, salt
15 concentration, and concentration of organic molecules, such as formamide, and is determined by methods that are well known to those skilled in the art. Probes or primers specific for *titin* nucleic acid molecules, preferably, have greater than 45% sequence identity, more preferably at least 55-75% sequence identity, still more preferably at least 75-85% sequence identity,
20 yet more preferably at least 85-99% sequence identity, and most preferably 100% sequence identity to the sequences of human (see below) or zebrafish *titin*.

Probes can be detectably-labeled, either radioactively or non-radioactively, by methods that are well-known to those skilled in the art.
25 Probes can be used for methods involving nucleic acid hybridization, such as nucleic acid sequencing, nucleic acid amplification by the polymerase chain reaction, single stranded conformational polymorphism (SSCP) analysis, restriction fragment polymorphism (RFLP) analysis, Southern

hybridization, northern hybridization, *in situ* hybridization, electrophoretic mobility shift assay (EMSA), and other methods that are well known to those skilled in the art.

A molecule, *e.g.*, an oligonucleotide probe or primer, a gene or
5 fragment thereof, a cDNA molecule, a polypeptide, or an antibody, can be said to be “detectably-labeled” if it is marked in such a way that its presence can be directly identified in a sample. Methods for detectably-labeling molecules are well known in the art and include, without limitation, radioactive labeling (*e.g.*, with an isotope, such as ^{32}P or ^{35}S)
10 and nonradioactive labeling (*e.g.*, with a fluorescent label, such as fluorescein).

By a “substantially pure polypeptide” is meant a polypeptide (or a fragment thereof) that has been separated from proteins and organic molecules that naturally accompany it. Typically, a polypeptide is
15 substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the polypeptide is a titin polypeptide that is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, pure. A substantially pure titin polypeptide can be obtained, for
20 example, by extraction from a natural source (*e.g.*, isolated heart tissue), by expression of a recombinant nucleic acid molecule encoding a titin polypeptide, or by chemical synthesis. Purity can be measured by any appropriate method, *e.g.*, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

25 A polypeptide is substantially free of naturally associated components when it is separated from those proteins and organic molecules that accompany it in its natural state. Thus, a protein that is chemically synthesized or produced in a cellular system different from the

cell in which it is naturally produced is substantially free from its naturally associated components. Accordingly, substantially pure polypeptides not only include those derived from eukaryotic organisms, but also those synthesized in *E. coli* or other prokaryotes.

5 An antibody is said to “specifically bind” to a polypeptide if it recognizes and binds to the polypeptide (*e.g.*, a titin polypeptide), but does not substantially recognize and bind to other molecules (*e.g.*, non-titin related polypeptides) in a sample, *e.g.*, a biological sample that naturally includes the polypeptide.

10 By “high stringency conditions” is meant conditions that allow hybridization comparable with the hybridization that occurs using a DNA probe of at least 500 nucleotides in length, in a buffer containing 0.5 M NaHPO₄, pH 7.2, 7% SDS, 1 mM EDTA, and 1% BSA (fraction V), at a temperature of 65°C, or a buffer containing 48% formamide, 4.8 x SSC, 15 0.2 M Tris-Cl, pH 7.6, 1 x Denhardt’s solution, 10% dextran sulfate, and 0.1% SDS, at a temperature of 42°C. (These are typical conditions for high stringency northern or Southern hybridizations.) High stringency hybridization is also relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high stringency PCR, 20 DNA sequencing, single strand conformational polymorphism analysis, and *in situ* hybridization. In contrast to northern and Southern hybridizations, these techniques are usually performed with relatively short probes (*e.g.*, usually 16 nucleotides or longer for PCR or sequencing and 40 nucleotides or longer for *in situ* hybridization). The high 25 stringency conditions used in these techniques are well known to those skilled in the art of molecular biology, and examples of them can be

found, for example, in Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1998, which is hereby incorporated by reference.

By "sample" is meant a tissue biopsy, amniotic fluid, cell, blood, serum, urine, stool, or other specimen obtained from a patient or test subject. The sample can be analyzed to detect a mutation in a *titin* gene, or expression levels of a *titin* gene, by methods that are known in the art. For example, methods such as sequencing, single-strand conformational polymorphism (SSCP) analysis, or restriction fragment length polymorphism (RFLP) analysis of PCR products derived from a patient sample can be used to detect a mutation in a *titin* gene; ELISA can be used to measure levels of titin polypeptide; and PCR can be used to measure the level of a *titin* nucleic acid molecule.

By "titin-related disease" or "titin-related condition" is meant a disease or condition that results from inappropriately high or low expression of a *titin* gene, or a mutation in a *titin* gene that alters the biological activity of a *titin* nucleic acid molecule or polypeptide. Titin-related diseases and conditions can arise in any tissue in which titin is expressed during prenatal or post-natal life. Titin-related diseases and conditions can include heart diseases, such as heart failure. Specific examples of different types of heart failure are provided below.

The invention provides several advantages. For example, using the diagnostic methods of the invention, it is possible to detect an increased likelihood of heart disease, such as heart failure, in a patient, so that appropriate intervention can be instituted before any symptoms occur. This may be useful, for example, with patients in high-risk groups for heart failure (see above). Also, the diagnostic methods of the invention facilitate determination of the etiology of an existing heart condition, such

as heart failure, in a patient, so that an appropriate approach to treatment can be selected. In addition, the screening methods of the invention can be used to identify compounds that can be used to treat or to prevent heart conditions, such as heart failure.

- 5 Other features and advantages of the invention will be apparent from the following detailed description and the claims.

Brief Description of the Drawing

Fig. 1 is a schematic representation of the domain structure of the human titin filament. The nucleotide and amino acid sequences of human
10 titin are provided in SEQ ID NOs:1 and 2, respectively. The modular architecture of cardiac titin as predicted by its full-length cDNA is shown.

A total of 244 copies of 100 residue repeats, as indicated by vertical rectangles, are contained in the molecule. One hundred and twelve of these belong to the Ig domain, and 132 belong to the FN3 superfamily.
15 The titin kinase domain, as well as the PEVK element N2-B 163-residue variant are also shown. Within the A-band, the D-zone contains six tandem repeats of the seven domains shown (A1 through A42), and the C-zone contains 11 tandem repeats of the 11 domains shown (A43 through A163). The positions of the tandemly repeated RMSP and VKSP motifs
20 in the Z-disc and M-line region are also shown

Detailed Description

The invention provides methods of diagnosing heart disease, screening methods for identifying compounds that can be used to treat or to prevent heart disease, and methods of treating or preventing heart

disease using these compounds. The invention also provides animal model systems that can be used in the screening methods of the invention.

In particular, we have discovered that a mutation (the *pickwick* mutation) in the *titin* gene is associated with heart disease, such as heart failure. Titin, which is also known as “connectin,” is the largest known single-chain protein, having a molecular weight of about 3,000 kDa. Titin is a structural protein, and plays a central role in the assembly and elasticity of vertebrate skeletal and cardiac muscle. Thus, the diagnostic methods of the invention involve detection of mutations in the *titin* gene, while the compound identification methods of the invention involve screening for compounds that affect the phenotype of *titin* mutants or other models of heart disease, such as heart failure. Compounds identified in this manner can be used in methods to treat or to prevent heart disease (e.g., heart failure). The diagnostic, screening, and therapeutic methods of the invention, as well as the animal model systems of the invention, are described further, as follows.

Diagnostic Methods

Titin nucleic acid molecules, polypeptides, and antibodies can be used in methods to diagnose or to monitor diseases and conditions involving mutations in, or inappropriate expression of, *titin* genes. As discussed further below, the *pickwick* mutation in zebrafish, which is present in the *titin* gene, is characterized by a phenotype that is similar to that of heart failure in humans. Thus, detection of abnormalities in *titin* genes or their expression can be used in methods to diagnose, or to monitor treatment or development of, human heart disease, such as heart failure. For use as references, the human cardiac *titin* cDNA sequence can be found at:

<http://www.embl-heidelberg.de/ExternalInfo/Titin/cardiacseq.html> (SEQ ID NO:1), while the corresponding protein sequence can be found at: <http://www.embl-heidelberg.de/ExternalInfo/Titin/cardiacpep.html> (SEQ ID NO:2).

5 As noted above, the diagnostic methods of the invention can be used, for example, with patients that have heart failure, in an effort to determine its etiology and, thus, to facilitate selection of an appropriate course of treatment. The diagnostic methods can also be used with patients that have not yet developed heart failure, but who are at risk of
10 developing such a disease, or with patients that are at an early stage of developing such a disease. Also, the diagnostic methods of the invention can be used in prenatal genetic screening, for example, to identify parents who may be carriers of a recessive *titin* mutation.

Examples of heart failure that can be diagnosed (and treated) using
15 the methods of the invention include congestive heart failure, which is characterized by fluid in the lungs or body, resulting from failure of the heart in acting as a pump; right sided heart failure (right ventricular), which is characterized by failure of the pumping action of the right ventricle, resulting in swelling of the body, especially the legs and
20 abdomen; left sided heart failure (left ventricular), which is caused by failure of the pumping action of the left side of the heart, resulting in congestion of the lungs; forward heart failure, which is characterized by the inability of the heart to pump blood forward at a sufficient rate to meet the oxygen needs of the body at rest or during exercise; backward heart
25 failure, which is characterized by the ability of the heart to meet the needs of the body only if heart filling pressures are abnormally high; low-output,

which is characterized by failure to maintain blood output; and high-output, which is characterized by heart failure symptoms, even when cardiac output is high.

Titin may also play a role in cardiovascular diseases other than heart failure, such as coronary artery disease or conditions associated with valve formation defects, and, thus, detection of abnormalities in *titin* genes or their expression can be used in methods to diagnose and monitor these conditions as well. The methods of the invention can be used to diagnose (or to treat) the disorders described herein in any mammal, for example, humans, domestic pets, or livestock.

Titin abnormalities that can be detected using the diagnostic methods of the invention include those characterized by, for example, (i) abnormal titin polypeptides, (ii) *titin* genes containing mutations that result in the production of such polypeptides, and (iii) *titin* mutations that result in production of abnormal amounts of titin. Detection of such abnormalities, thus, can be used in methods to diagnose human heart disease, such as heart failure. Exemplary of the *titin* mutations that can be detected using the methods of the invention is the *pickwick* mutation (see below).

Detection of *titin* mutations can be carried out using any diagnostic technique. For example, a biological sample obtained from a patient can be analyzed for one or more mutations in *titin* nucleic acid molecules (e.g., the *pickwick* mutation) using a mismatch detection approach. Generally, this approach involves polymerase chain reaction (PCR) amplification of nucleic acid molecules from a patient sample, followed by identification of a mutation (i.e., a mismatch) by detection of altered hybridization, aberrant electrophoretic gel migration, binding, or cleavage mediated by mismatch binding proteins, or by direct nucleic acid molecule sequencing. Any of

these techniques can be used to facilitate detection of mutant *titin* genes, and each is well known in the art. Examples of these techniques are described by Orita *et al.* (Proc. Natl. Acad. Sci. U.S.A. 86:2766-2770, 1989) and Sheffield *et al.* (Proc. Natl. Acad. Sci. U.S.A. 86:232-236, 5 1989).

Mutation detection assays also provide an opportunity to diagnose a titin-mediated predisposition to heart disease before the onset of symptoms. For example, a patient heterozygous for a *titin* mutation that suppresses normal titin biological activity or expression may show no 10 clinical symptoms of a titin-related disease, and yet possess a higher than normal probability of developing heart disease, such as heart failure. Given such a diagnosis, a patient can take precautions to minimize exposure to adverse environmental factors, and can carefully monitor their medical condition, for example, through frequent physical examinations. 15 As mentioned above, this type of diagnostic approach can also be used to detect *titin* mutations in prenatal screens.

The *titin* diagnostic assays described above can be carried out using any biological sample (for example, a muscle tissue sample) in which titin is normally expressed. Because of the limited number of tissues in which 20 titin is expressed, as well as the relative difficulties involved in obtaining samples of these tissues, it may be preferable to detect mutant *titin* genes in another, more easily obtained sample type, such as blood or amniotic fluid samples using, for example, mismatch detection techniques. Preferably, the DNA in such a sample is subjected to PCR amplification 25 prior to analysis.

Levels of titin expression in a patient sample can be determined by using any of a number of standard techniques that are well known in the art. For example, titin expression in a biological sample (*e.g.*, a blood or

tissue sample, or amniotic fluid) from a patient can be monitored by standard northern blot analysis or by quantitative PCR (see, *e.g.*, Ausubel *et al.*, *supra*; *PCR Technology: Principles and Applications for DNA Amplification*, H.A. Ehrlich, Ed., Stockton Press, NY; Yap *et al.*, Nucl. Acids. Res. 19:4294, 1991).

In yet another diagnostic approach of the invention, an immunoassay is used to detect or to monitor titin protein levels in a biological sample. Titin-specific polyclonal or monoclonal antibodies can be used in any standard immunoassay format (*e.g.*, ELISA, Western blot, RIA; see, *e.g.*, Ausubel *et al.*, *supra*) to measure titin polypeptide levels. These levels are compared to wild-type titin levels. For example, a decrease in titin production may be indicative of a condition or a predisposition to a condition involving insufficient titin biological activity.

Immunohistochemical techniques can also be utilized for titin detection. For example, a tissue sample can be obtained from a patient, sectioned, and stained for the presence of titin using an anti-titin antibody and any standard detection system (*e.g.*, one that includes a secondary antibody conjugated to horseradish peroxidase). General guidance regarding such techniques can be found in, *e.g.*, Bancroft *et al.*, *Theory and Practice of Histological Techniques*, Churchill Livingstone, 1982, and in Ausubel *et al.*, *supra*.

Identification of Molecules That Can Be Used to Treat or to Prevent Heart Failure

Identification of a mutation in *titin* as resulting in a phenotype that is related to heart failure facilitates the identification of molecules (*e.g.*, small organic molecules, peptides, or nucleic acid molecules) that can be

used to treat or to prevent heart failure. The effects of candidate compounds on heart failure can be investigated using, for example, the zebrafish system. The zebrafish, *Danio rerio*, is a convenient organism to use in genetic analysis of vascular development. In addition to its short
5 generation time and fecundity, it has an accessible and transparent embryo, allowing direct observation of blood vessel function from the earliest stages. As discussed further below, zebrafish and other animals having mutations in the *titin* gene, which can be used in these methods, are also included in the invention.

10 In one example of the screening methods of the invention, a zebrafish having a mutation in the *titin* gene (e.g., a zebrafish having the *pickwick* mutation; see below) is contacted with a candidate compound, and the effect of the compound on the development of a heart abnormality that is characteristic of heart failure, or on the status of such an existing
15 heart abnormality, is monitored, relative to an untreated, identically mutant control. As discussed further below, zebrafish having the *pickwick* mutation are characterized by, for example, reduction of peak systolic pressures, stretched and thin myocardium, excess cardiac jelly, absent A-V cushions, and an obstructed ventricular outflow tract. Thus, these
20 characteristics (in addition to other characteristics of heart failure) can be monitored using the screening methods of the invention.

After a compound has been shown to have a desired effect in the zebrafish system, it can be tested in other models of heart disease, for example, in mice or other animals having a mutation in the *titin* gene.
25 Alternatively, testing in such animal model systems can be carried out in the absence of zebrafish testing.

Candidate compounds can be purified (or substantially purified) molecules or can be one component of a mixture of compounds (e.g., an

extract or supernatant obtained from cells; Ausubel *et al.*, *supra*). In a mixed compound assay, the effect on a phenotype of heart failure is tested against progressively smaller subsets of the candidate compound pool (e.g., produced by standard purification techniques, e.g., HPLC or FPLC) until a single compound or minimal compound mixture is demonstrated to have the desired effect.

Test compounds that can be screened in the methods described above can be chemicals that are naturally occurring or artificially derived. Such compounds can include, for example, polypeptides, synthesized organic molecules, naturally occurring organic molecules, nucleic acid molecules, and components thereof. Candidate compound can be found, for example, in a cell extract, mammalian serum, or growth medium in which mammalian cells have been cultured.

In general, novel drugs for prevention or treatment of mutant titin-related heart diseases can be identified from large libraries of both natural products, synthetic (or semi-synthetic) extracts, and chemical libraries using methods that are well known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening methods of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using these methods. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic-, or animal-based extracts, fermentation broths, and synthetic compounds, as well as modifications of existing compounds.

Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid molecule-based compounds. Synthetic

compound libraries are commercially available from Brandon Associates (Merrimack, NH) and Aldrich Chemical (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceanographic Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries can be produced, if desired, according to methods known in the art, *e.g.*, by standard extraction and fractionation. Furthermore, if desired, any library or compound can be readily modified using standard chemical, physical, or biochemical methods.

In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (*e.g.*, taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their therapeutic activities for heart failure can be employed whenever possible.

When a crude extract is found to have an effect on the development or persistence of heart failure, further fractionation of the positive lead extract can be carried out to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract having a desired activity. The same assays described herein for the detection of activities in mixtures of compounds can be used to purify the active component and to test derivatives of these compounds. Methods of fractionation and purification of such heterogeneous extracts are well known in the art. If desired,

compounds shown to be useful agents for treatment can be chemically modified according to methods known in the art.

Treatment or Prevention of Heart Failure

- Compounds identified using the screening methods described above
- 5 can be used to treat patients that have or are at risk of developing heart disease, such as heart failure. Such treatment may be required only for a short period of time, or may, in some form, be required throughout a patient's lifetime. Any continued need for treatment, however, can be determined using, for example, the diagnostic methods described above.
- 10 In considering various therapies, it is understood that such therapies are, preferably, targeted to the affected or potentially affected organ, that is, the heart.

Treatment or prevention of diseases resulting from a mutated *titin* gene can be accomplished, for example, by modulating the function of a

15 mutant *titin* protein, delivering normal *titin* protein to the appropriate cells, altering the levels of normal or mutant *titin* protein, replacing a mutant *titin* gene with a normal *titin* gene or, administering a normal *titin* gene. It is also possible to correct a *titin* defect by modifying the physiological pathway (*e.g.*, a signal transduction pathway) in which the *titin* protein

20 participates.

In a patient diagnosed as heterozygous for a *titin* mutation, or as susceptible to *titin* mutations or aberrant *titin* expression (even if those mutations or expression patterns do not yet result in alterations in *titin* expression or biological activity), any of the above-described therapies can

25 be administered before the occurrence of the disease phenotype. In particular, compounds shown to modulate *titin* expression or to have an

effect on the phenotype of *titin* mutants can be administered to patients diagnosed with potential or actual heart disease by any standard dosage and route of administration.

Any appropriate route of administration can be employed to
5 administer a compound found to be effective in treating or preventing heart failure, according to the invention. For example, administration can be parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, or oral. However, as noted above, preferably, the
10 administration is local to the afflicted tissue, that is, the heart. Therapeutic formulations can be in the form of liquid solutions or suspensions; for oral administration, formulations can be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

15 A therapeutic compound of the invention can be administered within a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Administration can begin before or after the patient is symptomatic. Methods that are well known in the art for making formulations are found, for example, in *Remington's Pharmaceutical*
20 *Sciences*, (18th edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, PA. Formulations for parenteral administration can, for example, contain excipients; sterile water; or saline; polyalkylene glycols, such as polyethylene glycol; oils of vegetable origin; or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide
25 copolymer, or polyoxyethylene-polyoxypropylene copolymers can be used to control the release of the compounds. Other potentially useful parenteral delivery systems for compounds identified using the methods of the invention include ethylene-vinyl acetate copolymer particles, osmotic

pumps, implantable infusion systems, and liposomes. Formulations for inhalation can contain excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate, and deoxycholate, or can be oily solutions for administration
5 in the form of nasal drops, or as a gel.

Titin nucleic acid molecules and polypeptides can also be used in tissue engineering, for example, in the manufacture of artificial or partially artificial hearts. As mentioned above, titin plays a role in cardiovascular elasticity, integrity, and contractility. Thus, a *titin* nucleic acid molecule
10 or polypeptide, as described above, can be used to impart such characteristics on an artificial or partially artificial heart.

Animal Model Systems

The invention also provides animal model systems for use in carrying out the screening methods described above. Examples of these
15 model systems include zebrafish and other animals, such as mice, that have mutations in a *titin* gene. For example, a zebrafish model that can be used in the invention can include a mutation that results in a lack of titin production or production of a truncated (*e.g.*, by introduction of a stop codon) or otherwise altered titin gene product. The mutation can, for
20 example, result in the presence of a stop codon in a cardiac-specific exon, such as the N2B exon (*e.g.*, in the IS3 region; see below). The mutation can be in a region encoding the I band, resulting in the production of a protein in which the I band is truncated and the A band and M line are absent, or can be in a region encoding another portion of the molecule,
25 such as the A band or M line region. As a specific example, a zebrafish having the *pickwick* mutation can be used.

Experimental Results

During a large-scale mutagenesis screening of the zebrafish genome, a group of mutations were identified that affect cardiac contractility. One of these mutations, called *pickwick* (*pik*), dramatically
5 reduces the function of both chambers, causing a recessive, lethal form of heart failure in the zebrafish embryo.

Direct *in vivo* recording of ventricular pressures by the null balance feedback system shows that *pickwick* causes a 5.8 fold reduction of peak systolic pressures, compared to age-matched controls (0.084 ± 0.008 vs.
10 0.49 ± 0.06 mm Hg). Morphological analysis of *pickwick* revealed a stretched and thin myocardium, excess cardiac jelly, absent A-V cushions, and an obstructed ventricular outflow tract. Extensive ultrastructural defects were found by transmission electron microscopy, affecting the assembly of Z-discs and the organization of myofilaments. Reciprocal
15 blastomere transplants identified *pickwick* as a cell autonomously acting mutation of the myoblast lineage.

A positional cloning approach was adopted for gene identification. The *pickwick* mutation has been assigned to a small chromosomal interval, which is covered by BAC clones. The *titin* gene spans this interval, and
20 thus the *pickwick* phenotype is due to a mutation in the *titin* gene. In particular, the *pickwick* gene was mapped to linkage group (LG) 9 by bulk segregant analysis using the *pikm242* allele, which is one of five cardiac specific alleles (*pikm242*, *pikm171*, *pikm740*, *pikm186*, *pikmnm2*). A panel of Z-markers in the linkage group was tested for simple sequence
25 length polymorphisms (SSLPs) using 931 homozygous mutant embryos. Markers Z8363 and Z26463 were shown to flank the *pickwick* locus, defining a 1.2 cM interval containing the gene. It is estimated that 1 cM corresponds to 500-600 kb DNA in the zebrafish genome (Postlethwait *et*

al., Science 264:699-703, 1994). We thus initiated chromosomal walking from the Z8363 marker, which is 0.7 cM from the mutation (12 recombinants out of 1750 meioses).

A positive YAC clone (YAC5) was identified that had a T7 end that
5 is highly homologous to human *titin* coding sequences. As the *titin* genomic region was estimated to be over 300 kb in humans, we decided to identify BAC clones based on sequence information of the zebrafish *titin* EST clones. A physical contig was constructed based on these sequences, which covers the whole *titin* genomic area. Single stranded
10 conformational polymorphisms (SSCPs) were developed from the ends and internal sequences of these clones were used for fine recombinational mapping. One SSCP marker inside the *titin* genomic area (B9F2) picked up one recombinant from the Z26463 side. The other four SSCP markers inside the *titin* genomic area (B4SP1, B2T7, B7SP, and B6SP) picked up
15 zero recombinants out of 1750 meioses. These genetic data indicated that the *pickwick* locus is very close to or within the *titin* genomic region.

As the *titin* cDNA alone is around 82 kb, rescuing the phenotype by RNA injection could prove to be quite difficult. However, we found evidence that the *pickwick* locus is within the *titin* gene by identification of
20 point mutations in one of the *pickwick* alleles. As most of the alleles of *pickwick* have a cardiac-specific phenotype, we presumed that the point mutation is located in a cardiac-specific exon. We focused on the N2B domain in the I-band of titin, as all of the cardiac isoforms are N2B domain based. The zebrafish N2B domain was cloned by RT-PCR. It is a
25 4.3 kb cDNA encoding infrastructures similar to those in humans and mice, and contains 4 IG repeats and three unique sequences, including longer IS3 and shorter IS1.

N2B domains from *pickwick* mutant embryos were then cloned. RNA mismatch analysis was performed to identify the location of the point mutation. One mismatch between the PCR products from *pikm171* and *pikm242* was identified. Sequencing of the PCR product resulted in the identification of a T-> G transition in the *pikm171* allele. This mutation resulted in a change of leucine in the IS3 fragment of N2B domain (N2B-IS3) into a stop codon. The mutation was confirmed in all of the seven homozygous *pikm171* mutant embryos, but none of the four *pikm242* homozygous embryos. A truncated version of titin is predicted to be in the *pikm171* mutant, only as a cardiac specific isoform. It should contain the Z-disc and part of the I-band and be sized around 4,000 amino acids, based on comparison to the homologous human titin sequence, which has a full length of 27,000 amino acids. The identification of a non-sense mutation in the cardiac specific N2B domain in *pikm171* allele confirmed the hypothesis that *titin* is the *pickwick* gene.

Titin was expressed in the zebrafish embryo during the period when the *pickwick* phenotype was first detected. Whole mount *in situ* hybridization analysis indicated that *titin* was expressed strongly in both the heart and the somites at 24 hpf. *Titin* mRNA expression in the heart is normal in *pikm171*. We confirmed the notion that N2B is a cardiac-specific exon in zebrafish by labeling a probe in the IS3 domain for the whole mount *in situ* hybridization.

The identification of a point mutation in the N2B domain thus establishes *pickwick* as the first *in vivo* vertebrate system to study the functions of titin in the heart. If titin functions as a spring, as proposed, it is expected that the contraction will be much weaker. This is exactly what we observed in *pickwick* mutant embryos. If titin functions as a template during the sarcomere assembly, a "silent heart" phenotype would be

expected in titin null mutation. According to the current model of the myofibrillogenesis (Dabiri *et al.*, Proc. Natl. Acad. Sci. U.S.A. 94:9493-9498, 1997), the thick element and/or the sarcomere could not assemble into a beating machine. In contrast, the hearts in the homozygous *pikm171* mutant embryos and all of the other *pickwick* alleles still beat, despite being weaker.

The mutation in *pikm171* predicts a truncated protein in which most of the elastic I-band is deleted and the C-terminal A-band and M-line regions eliminated. It thus could be considered as a null mutation in terms of function as a spring and a potential dominant negative mutation in terms of its function as a template for sarcomere assembly (Turnacioglu *et al.*, Mol. Biol. Cell 8:705-717, 1997). The observation of the weak beating in the *pickwick* mutant embryos suggested the existence of primary contractile machinery without titin. Indeed, thick and thin elements can be detected in the ventricular myocardium cells. They have the capacity to assemble into a functional beating structure in the absence of titin.

We thus have carried out a detailed physiological and morphological analysis of *pickwick*, a zebrafish heart function mutation that reduces the contractility of both chambers. Several pieces of evidence pointed out that *titin* is the *pickwick* gene. Genetic analysis linked the *pickwick* locus closely to the *titin* genomic area. The identification of the *pikmVO62H*, a *pickwick* allele that has an additional somite phenotype, can be explained by the titin hypothesis. The point mutation is expected to be in the common exons that are shared between the cardiac and somatic isoforms of titin. Evidence confirming this hypothesis came from the identification of a point mutation in the cardiac specific N2B domain of titin in one of the *pickwick* alleles, *pikm171*. We went on to show that sarcomere structure is disrupted in the myocardium cells of *pikm171*, but

not the somatic muscle cells. The expression pattern of titin is consistent with this phenotype. Strong expression in both cardiac and skeletal muscles was detected at the onset of the *pickwick* phenotype.

Thus, our observation in zebrafish is in consistent with the notion
5 that titin functions as a spring during the muscle contraction. As titin is a sarcomere structure protein, it is conceivable that myocardium is affected cell-autonomously in *pickwick* mutant embryos. The thin and stretched morphology could be due to the mechanic tension generated from the failure to form higher-order sarcomere structure and the loss of spring.
10 The mechanic tension may also be the reason for the separation between the myocardium cells and endocardium cells, generating the excess cardiac jelly. However, there is a possibility that the differentiation program of the myocardium was affected in the *titin* mutation. The valve formation phenotype in *pickwick* mutant embryos could be a secondary defect. It has
15 been suggested that the process of endothelial invasion during valve formation is under control of a localized myocardial signal. (For a review, see Fishman *et al.*, Development 124:2099-2117, 1997.) The physical distance between myocardium and endocardium and/or the stalked differential program in the myocardium could be the reason that prevents a
20 normal cushion formation.

Material and Methods

Zebrafish strains and maintenance

Zebrafish were maintained and staged as described. *pikm242*,
pikm171, *pikm740*, *pikm186* were generated in a screen on the AB
25 background (Stainier *et al.*, Development 123:285-292, 1996).
pikmVO62H and *pikmnml2* were generated in a screen on the TL background. Mapping strains were constructed by crossing *pikm242* into

india strain. *pikm171* embryos used in expression analysis and EM were obtained from pair wise matings of *pikm171*/TL heterozygotes.

In situ hybridization

Whole mount *in situ* hybridization was performed as described
5 (Thisse *et.al.*, Development 119:1203-1215, 1993). T5 probe was generated by digestion of the EST clone AI629069 (Research Genetics). The N2B and N2A probe were generated through PCR with a tagged T7 promoter. The primer pairs are:
P238F: 5'-AGGGACACTCAGAGACCATAG (SEQ ID NO:3); and
10 P3785RT: 5'-
TAATACGACTCACTATAGGGGTCTGAGGATACTCGCCTTC (SEQ ID NO:4).

Mapping of *pickwick*

Linkage was established using DNA from 16 homozygous
15 mutations and 16 heterozygous or wild type pick *pikm242*/indian embryos in bulk segregation analysis (Michelmore *et al.*, Proc. Natl. Acad. Sci. U.S.A. 88:9828-9832, 1991). Z-markers (simple sequence length polymorphisms, SSLP) were developed in this lab (Knapik *et al.*, Nat. Genet. 18:338-343, 1998; Shimoda *et al.*, Genomics 58:219-232, 1999).
20 Genotyping products were resolved in 6% PAGE gels.

Chromosomal walking

YAC and BAC clones were screened by PCR as pools of clones (Research Genetics) according to the manufacturer's instruction. YAC ends were cloned by plasmid rescue (Zhong *et al.*, Genomics 48:136-138,
25 1998). Chimeric ends were determined by the RH panel (Geisler *et al.*,

Nat. Genet. 23:86-89, 1999). BAC DNA was extracted using the QIAgene kit and the end sequences were determined by direct sequencing. BLAST-X was performed to search for homologous sequence in Genebank. EST clones were generated by Washington University zebrafish EST project and obtained from Research Genetics. Oligonucleotides derived from the end sequences of YAC and BAC clones were used in standard PCR reactions to determine clone overlap. Primer pair B9F2 was derived from a fragment that was generated by digesting BAC5 with BamHI and then subcloning into the pUC19 vector. This clone can be hit by a primer pair derived from the T7 end of BAC7. Single-strand conformation polymorphisms (SSCP) were tested on 6% MDE acrylamide (FMC Bioproducts) gels at 40°C.

Cloning of the zebrafish N2B domain

Long RT-PCR was performed to amplify the N2B domain from adult zebrafish heart mRNA extracts. mRNA was extracted from pools of ten zebrafish adult hearts using TRIzol reagent (GibcoBRL), as described. The cDNA was synthesized using SuperScriptTMII RNase H-Reverse Transcriptase (GibcoBRL) and then treated with RNase H. The primer is derived from EST3: I19R1:

5'- TTTGAACCACTTGAAGGTCACACCAGG (SEQ ID NO:5).

Long-PCR was performed using Expand 20kbPlus PCR System (Roch) as described. The primer pairs are:

I14F1: 5'- GCTAAGAATGACTATGGAGTTGCCACAAGC (SEQ ID NO:6)

I19R2: 5'- TGAACCACTTGAAGGTCACACCAGGAG (SEQ ID NO:7)

The 4.6 kb product was subcloned using TOPO TA Cloning Kit (Invitrogen) as described. The sequence was determined by primer walking. Forty eight reads were aligned by Phred/Phrad software to get a large contig that contains only one reading frame with around three fold
5 coverage.

To amplify the N2B region from the homozygous mutant zebrafish embryos, three overlapping primer pairs were designed according to the adult N2B sequence. The contamination from the skeletal muscle specific titin isoform was thus eliminated. mRNA was extracted from pools of ten
10 zebrafish day 2 embryos using TRIzol reagent (GibcoBRL) as described. Sequencing results indicated that the embryonic heart titin contain one less IG domain in the area.

Identification of the point mutation

N2B domains from the homozygous mutant embryos were further
15 amplified by primer pairs that generate six overlapping PCR products sized between 0.6 kb and about 1 kb. RNA mismatch analysis was performed using MutationScreenerTM (Ambion) according to the manufacture's protocol. A mismatch was identified between *pikm171* and *pikm242* using the primer pairs:

20 P238FT:

5'-TAATACGACTCACTATAGGGAGGGACACTCAGAGACCATAG
(SEQ ID NO:8)

P3785RT: 5'-

TAATACGACTCACTATAGGGGTCTGAGGATACTCGCCTTC (SEQ
25 ID NO:9). Sequencing results indicate a T->G non-sense mutation in the cDNA from homozygous *pikm171* embryos.

Genomic sequence in this region was amplified using the primer pair:

P238F: 5'-AGGGACACTCAGAGACCATAG (SEQ ID NO:10)

P341R: 5'- GGCAATGTTACTCTCTGTTGAG (SEQ ID NO:11)

and sent out directly for sequencing after purification using the Geneclean Spin Kit (BIO101).

5 Electron Microscopy

Forty eight hour embryos were fixed overnight at 4°C in 1.5% glutaraldehyde, 1% paraformaldehyde, 70 mM NaPO₄ pH 7.2, 3% Sucrose. They were then washed 3 times for 5 minutes each in 0.1M cacodylate buffer, pH 7.4.

10 Other Embodiments

Although the present invention has been described with reference to preferred embodiments, one skilled in the art can easily ascertain its essential characteristics and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the present invention.

20 All publications and patents mentioned in this specification are hereby incorporated by reference.

What is claimed is:

Claims

1. A method of determining whether a test subject has, or is at risk of developing, a titin-related disease or condition, said method comprising analyzing a nucleic acid molecule of a sample from the test subject to
5 determine whether the test subject has a mutation in a *titin* gene, wherein the presence of said mutation is an indication that said test subject has, or is at risk of developing, a titin-related disease.
2. The method of claim 1, further comprising the step of using nucleic acid molecule primers specific for the *titin* gene for nucleic acid
10 molecule amplification of the *titin* gene by the polymerase chain reaction.
3. The method of claim 1, further comprising the step of sequencing *titin* nucleic acid molecules from said test subject.
4. The method of claim 1, wherein said test subject is a mammal.
5. The method of claim 1, wherein said test subject is human.
- 15 6. The method of claim 1, wherein said disease or condition is heart failure.
7. The method of claim 1, wherein said mutation is the *pickwick* mutation.

8. A method for identifying a compound that can be used to treat or to prevent heart failure, said method comprising contacting an organism comprising a *titin* mutation and having a phenotype characteristic of heart failure with said compound, and determining the effect of said compound on said phenotype, wherein detection of an improvement in said phenotype indicates the identification of a compound that can be used to treat or to prevent heart failure.
9. The method of claim 8, wherein said organism is a zebrafish.
10. The method of claim 8, wherein said *titin* mutation is the *pickwick* mutation.
11. A method of treating or preventing heart failure in a patient, said method comprising administering to said patient a compound identified using the method of claim 8.
12. The method of claim 11, wherein said patient has a mutation in the *titin* gene.
13. The method of claim 12, wherein said mutation is the *pickwick* mutation.
14. A non-human animal comprising a mutation in a *titin* gene.
15. The non-human animal of claim 14, wherein the non-human animal is a zebrafish.

16. The non-human animal of claim 14, wherein the mutation is in a cardiac-specific exon of said *titin* gene.

17. The non-human animal of claim 16, wherein the mutation is in the N2B exon of said *titin* gene.

5 18. The non-human animal of claim 14, wherein the mutation results in the presence of a stop codon in said *titin* gene.

19. The non-human animal of claim 14, wherein the mutation is the *pickwick* mutation.

DOMAIN STRUCTURE OF HUMAN CARDIAC TITIN

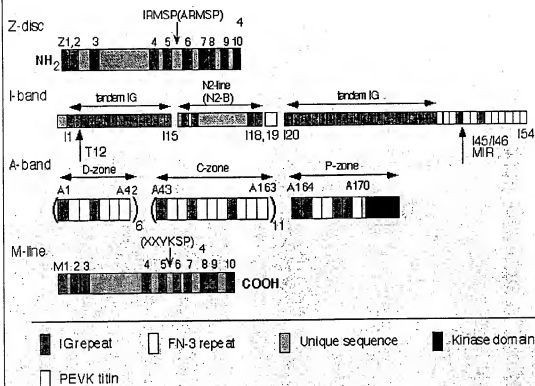


Fig. 1 Domain structure of the titin filament.

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<212> PRT

<213> Homo sapiens

<400> 2

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Pro Val Pro Glu Val Ser Trp Phe Arg Asp Gly Gln Val Ile Ser Thr
 35          40          45
Ser Thr Leu Pro Gly Val Gln Ile Ser Phe Ser Asp Gly Arg Ala Lys
 50          55          60
Leu Thr Ile Pro Ala Val Thr Lys Ala Asn Ser Gly Arg Tyr Ser Leu
 65          70          75
Lys Ala Thr Asn Gly Ser Gly Gln Ala Thr Ser Thr Ala Glu Leu Leu
 85          90          95
Val Lys Ala Glu Thr Ala Pro Pro Asn Phe Val Gln Arg Leu Gln Ser
100          105          110
Met Thr Val Arg Gln Gly Ser Gln Val Arg Leu Gln Val Arg Val Thr
115          120          125
Gly Ile Pro Thr Pro Val Val Lys Phe Tyr Arg Asp Gly Ala Glu Ile
130          135          140
Gln Ser Ser Leu Asp Phe Gln Ile Ser Gln Glu Gly Asp Leu Tyr Ser
145          150          155
Leu Leu Ile Ala Glu Ala Tyr Pro Glu Asp Ser Gly Thr Tyr Ser Val
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Asn Ala Thr Asn Ser Val Gly Arg Ala Thr Ser Thr Ala Glu Leu Leu
180          185          190
Val Gln Gly Glu Glu Glu Val Pro Ala Lys Lys Thr Lys Thr Ile Val
195          200          205
Ser Thr Ala Gln Ile Ser Glu Ser Arg Gln Thr Arg Ile Glu Lys Lys
210          215          220

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Ala Lys Ala Gln Leu Ala Arg Gln Gln Ser Pro Ser Pro Ile Arg His
      275      280      285
Ser Pro Ser Pro Val Arg His Val Arg Ala Pro Thr Pro Ser Pro Val
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Gln Val Thr His Gly Lys Val Asp Val Gly Lys Lys Ala Glu Ala Val
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Ala Thr Val Val Ala Ala Val Asp Gln Ala Arg Val Arg Glu Pro Arg
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Glu Pro Gly His Leu Glu Glu Ser Tyr Ala Gln Gln Thr Thr Leu Glu
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Tyr Gly Tyr Lys Glu Arg Ile Ser Ala Ala Lys Val Ala Glu Pro Pro
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Gln Arg Pro Ala Ser Glu Pro His Val Val Pro Lys Ala Val Lys Pro
705      710      715      720

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Arg Val Ile Gln Ala Pro Ser Glu Thr His Ile Lys Thr Thr Asp Gln
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 Ser Val Thr Leu Glu Cys His Ile Ser Gly Tyr Pro Ser Pro Thr Val
 915 920 925
 Thr Trp Tyr Arg Glu Asp Tyr Gln Ile Glu Ser Ser Ile Asp Phe Gln
 930 935 940
 Ile Thr Phe Gln Ser Gly Ile Ala Arg Leu Met Ile Arg Glu Ala Phe
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 Glu Lys Glu Thr Thr Ala Val Thr Glu Lys Phe Thr Thr Glu Glu Lys
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 Ala Leu Gly Leu Ser Thr Ser Gly Arg Val Ser Val Tyr Ser Val Asp
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 Val Ile Thr Pro Leu Lys Asp Val Asn Val Ile Glu Gly Thr Lys Ala
 2405 2410 2415
 Val Leu Glu Cys Lys Val Ser Val Pro Asp Val Thr Ser Val Lys Trp
 2420 2425 2430
 Tyr Leu Asn Asp Glu Gln Ile Lys Pro Asp Asp Arg Val Gln Ala Ile
 2435 2440 2445
 Val Lys Gly Thr Lys Gln Arg Leu Val Ile Asn Arg Thr His Ala Ser
 2450 2455 2460
 Asp Glu Gly Pro Tyr Lys Leu Ile Val Gly Arg Val Glu Thr Asn Cys
 2465 2470 2475 2480
 Asn Leu Ser Val Glu Lys Ile Lys Ile Ile Arg Gly Leu Arg Asp Leu
 2485 2490 2495
 Thr Cys Thr Glu Thr Gln Asn Val Val Phe Glu Val Glu Leu Ser His
 2500 2505 2510
 Ser Gly Ile Asp Val Leu Trp Asn Phe Lys Asp Lys Glu Ile Lys Pro
 2515 2520 2525
 Ser Ser Lys Tyr Lys Ile Glu Ala His Gly Lys Ile Tyr Lys Leu Thr
 2530 2535 2540
 Val Leu Asn Met Met Lys Asp Asp Glu Gly Lys Tyr Thr Phe Tyr Ala
 2545 2550 2555 2560
 Gly Glu Asn Met Thr Ser Gly Lys Leu Thr Val Ala Gly Gly Ala Ile
 2565 2570 2575
 Ser Lys Pro Leu Thr Asp Gln Thr Val Ala Glu Ser Gln Glu Ala Val
 2580 2585 2590
 Phe Glu Cys Glu Val Ala Asn Pro Asp Ser Lys Gly Glu Trp Leu Arg
 2595 2600 2605
 Asp Gly Lys His Leu Pro Leu Thr Asn Asn Ile Arg Ser Glu Ser Asp
 2610 2615 2620
 Gly His Lys Arg Arg Leu Ile Ile Ala Ala Thr Lys Leu Asp Asp Ile
 2625 2630 2635 2640
 Gly Glu Tyr Thr Tyr Lys Val Ala Thr Ser Lys Thr Ser Ala Lys Leu
 2645 2650 2655
 Lys Val Glu Ala Val Lys Ile Lys Lys Thr Leu Lys Asn Leu Thr Val
 2660 2665 2670
 Thr Glu Thr Gln Asp Ala Val Phe Thr Val Glu Leu Thr His Pro Asn
 2675 2680 2685
 Val Lys Gly Val Gln Trp Ile Lys Asn Gly Val Val Leu Glu Ser Asn
 2690 2695 2700

Glu Lys Tyr Ala Ile Ser Val Lys Gly Thr Ile Tyr Ser Leu Arg Ile 2705
 Lys Asn Cys Ala Ile Val Asp Glu Ser Val Tyr Gly Phe Arg Leu Gly 2720
 2725 2730 2735
 Arg Leu Gly Ala Ser Ala Arg Leu His Val Glu Thr Val Lys Ile Ile 2740
 2745 2750
 Lys Lys Pro Lys Asp Val Thr Ala Leu Glu Asn Ala Thr Val Ala Phe 2755
 2760 2765
 Glu Val Ser Val Ser His Asp Thr Val Pro Val Lys Trp Phe His Lys 2770
 2775 2780
 Ser Val Glu Ile Lys Pro Ser Asp Lys His Arg Leu Val Ser Glu Arg 2785
 2790 2795 2800
 Lys Val His Lys Leu Met Leu Gln Asn Ile Ser Pro Ser Asp Ala Gly 2805
 2810 2815
 Glu Tyr Thr Ala Val Val Gly Gln Leu Glu Cys Lys Ala Lys Leu Phe 2820
 2825 2830
 Val Glu Thr Leu His Ile Thr Lys Thr Met Lys Asn Ile Glu Val Pro 2835
 2840 2845
 Glu Thr Lys Thr Ala Ser Phe Glu Cys Glu Val Ser His Phe Asn Val 2850
 2855 2860
 Pro Ser Met Trp Leu Lys Asn Gly Val Glu Ile Glu Met Ser Glu Lys 2865
 2870 2875 2880
 Phe Lys Ile Val Val Gln Gly Lys Leu His Gln Leu Ile Ile Met Asn 2885
 2890 2895
 Thr Ser Thr Glu Asp Ser Ala Glu Tyr Thr Phe Val Cys Gly Asn Asp 2900
 2905 2910
 Gln Val Ser Ala Thr Leu Thr Val Thr Pro Ile Met Ile Thr Ser Met 2915
 2920 2925
 Leu Lys Asp Ile Asn Ala Glu Glu Lys Asp Thr Ile Thr Phe Glu Val 2930
 2935 2940
 Thr Val Asn Tyr Glu Gly Ile Ser Tyr Lys Trp Leu Lys Asn Gly Val 2945
 2950 2955 2960
 Glu Ile Lys Ser Thr Asp Lys Cys Gln Met Arg Thr Lys Lys Leu Thr 2965
 2970 2975
 His Ser Leu Asn Ile Arg Asn Val His Phe Gly Asp Ala Ala Asp Tyr 2980
 2985 2990
 Thr Phe Val Ala Gly Lys Ala Thr Ser Thr Ala Thr Leu Tyr Val Glu 2995
 3000 3005
 Ala Arg His Ile Glu Phe Arg Lys His Ile Lys Asp Ile Lys Val Leu 3010
 3015 3020
 Glu Lys Lys Arg Ala Met Phe Glu Cys Glu Val Ser Glu Pro Asp Ile 3025
 3030 3035 3040
 Thr Val Gln Trp Met Lys Asp Asp Gln Glu Leu Gln Ile Thr Asp Arg 3045
 3050 3055
 Ile Lys Ile Gln Lys Glu Lys Tyr Val His Arg Leu Leu Ile Pro Ser 3060
 3065 3070
 Thr Arg Met Ser Asp Ala Gly Lys Tyr Thr Val Val Ala Gly Gly Asn 3075
 3080 3085
 Val Ser Thr Ala Lys Leu Phe Val Glu Gly Arg Asp Val Arg Ile Arg 3090
 3095 3100
 Ser Ile Lys Lys Glu Val Gln Val Ile Glu Lys Gln Arg Ala Val Val 3105
 3110 3115 3120
 Glu Phe Glu Val Asn Glu Asp Asp Val Asp Ala His Trp Tyr Lys Asp 3125
 3130 3135
 Gly Ile Glu Ile Asn Phe Gln Val Gln Glu Arg His Lys Tyr Val Val 3140
 3145 3150
 Glu Arg Arg Ile His Arg Met Phe Ile Ser Glu Thr Arg Gln Ser Asp 3155
 3160 3165
 Ala Gly Glu Tyr Thr Phe Val Ala Gly Arg Asn Arg Ser Ser Val Thr 3170
 3175 3180
 Leu Tyr Val Asn Ala Pro Glu Pro Pro Gln Val Leu Gln Glu Leu Gln 3185
 3190 3195 3200

Pro	Val	Thr	Val	Aln	Ser	Gly	Lys	Pro	Ala	Arg	Phe	Cys	Ala	Met	Ile
Ser	Gly	Arg	Pro	Gln	Pro	Lys	Ile	Ser	Trp	Tyr	Lys	Glu	Glu	Gln	Leu
Leu	Ser	Thr	Gly	Phe	Lys	Cys	Lys	Phe	Leu	His	Asp	Gly	Gln	Glu	Tyr
Thr	Leu	Leu	Leu	Ile	Glu	Ala	Phe	Pro	Glu	Asp	Ala	Ala	Val	Tyr	Thr
Cys	Glu	Ala	Lys	Asn	Asp	Tyr	Gly	Val	Ala	Thr	Thr	Ser	Ala	Ser	Leu
Ser	Val	Glu	Val	Pro	Glu	Val	Val	Ser	Pro	Asp	Gln	Glu	Met	Pro	Val
Tyr	Pro	Pro	Ala	Ile	Ile	Thr	Pro	Leu	Gln	Asp	Thr	Val	Thr	Ser	Glu
Gly	Gln	Pro	Ala	Arg	Phe	Gln	Cys	Arg	Val	Ser	Gly	Thr	Asp	Leu	Lys
Val	Ser	Trp	Tyr	Ser	Lys	Asp	Lys	Lys	Ile	Lys	Pro	Ser	Arg	Phe	Phe
Arg	Met	Thr	Gln	Phe	Glu	Asp	Thr	Tyr	Gln	Leu	Glu	Ile	Ala	Glu	Ala
Tyr	Pro	Glu	Asp	Glu	Gly	Thr	Tyr	Thr	Phe	Val	Ala	Asn	Asn	Ala	Val
Gly	Gln	Val	Ser	Ser	Ser	Thr	Ala	Asn	Leu	Ser	Leu	Glu	Ala	Pro	Glu
Ile	Leu	His	Glu	Arg	Ile	Glu	Gln	Glu	Ile	Glu	Met	Glu	Met	Lys	Glu
Phe	Ser	Ser	Ser	Phe	Leu	Ser	Ala	Glu	Glu	Glu	Gly	Leu	His	Ser	Ala
Glu	Leu	Gln	Leu	Ser	Lys	Ile	Asn	Glu	Thr	Leu	Glu	Leu	Leu	Ser	Glu
Ser	Pro	Val	Tyr	Pro	Thr	Lys	Phe	Asp	Ser	Glu	Lys	Glu	Gly	Thr	Gly
Pro	Ile	Phe	Ile	Lys	Glu	Val	Ser	Asn	Ala	Asp	Ile	Ser	Met	Gly	Asp
Val	Ala	Thr	Leu	Ser	Val	Thr	Val	Ile	Gly	Ile	Pro	Lys	Pro	Lys	Ile
Gln	Trp	Phe	Phe	Asn	Gly	Val	Leu	Leu	Thr	Pro	Ser	Ala	Asp	Tyr	Lys
Phe	Val	Phe	Asp	Gly	Asp	Asp	His	Ser	Leu	Ile	Ile	Leu	Phe	Thr	Lys
Leu	Glu	Asp	Glu	Gly	Glu	Tyr	Thr	Cys	Met	Ala	Ser	Asn	Asp	Tyr	Gly
Lys	Thr	Ile	Cys	Ser	Ala	Tyr	Leu	Lys	Ile	Asn	Ser	Lys	Gly	Glu	Gly
His	Lys	Asp	Thr	Glu	Ser	Glu	Ser	Ala	Val	Ala	Lys	Ser	Leu	Glu	Lys
Leu	Gly	Gly	Pro	Cys	Pro	Pro	His	Phe	Leu	Lys	Glu	Leu	Lys	Pro	Ile
Arg	Cys	Ala	Gln	Gly	Leu	Pro	Ala	Ile	Phe	Glu	Tyr	Thr	Val	Val	Gly
Glu	Pro	Ala	Pro	Thr	Val	Thr	Trp	Phe	Lys	Glu	Asn	Lys	Gln	Leu	Cys
Thr	Ser	Val	Tyr	Tyr	Thr	Ile	Ile	His	Asn	Pro	Asn	Gly	Ser	Gly	Thr
Phe	Ile	Val	Asn	Asp	Pro	Gln	Arg	Glu	Asp	Ser	Gly	Leu	Tyr	Ile	Cys
Lys	Ala	Glu	Asn	Met	Leu	Gly	Glu	Ser	Thr	Cys	Ala	Ala	Glu	Leu	Leu
Val	Leu	Leu	Glu	Asp	Thr	Asp	Met	Thr	Asp	Thr	Pro	Cys	Lys	Ala	Lys
Ser	Thr	Pro	Glu	Ala	Pro	Glu	Asp	Phe	Pro	Gln	Thr	Pro	Leu	Lys	Gly

Pro Ala Val Glu Ala Leu Asp Ser Glu Gln Glu Ile Ala Thr Phe Val
 3700 3705 3710
 Lys Asp Thr Ile Leu Lys Ala Ala Leu Ile Thr Glu Glu Asn Gln Gln
 3715 3720 3725
 Leu Ser Tyr Glu His Ile Ala Lys Ala Asn Glu Leu Ser Ser Gln Leu
 3730 3735 3740
 Pro Leu Gly Ala Gln Glu Leu Gln Ser Ile Leu Glu Gln Asp Lys Leu
 3745 3750 3755 3760
 Thr Pro Glu Ser Thr Arg Glu Phe Leu Cys Ile Asn Gly Ser Ile His
 3765 3770 3775
 Phe Gln Pro Leu Lys Glu Pro Ser Pro Asn Leu Gln Leu Gln Ile Val
 3780 3785 3790
 Gln Ser Gln Lys Thr Phe Ser Lys Glu Gly Ile Leu Met Pro Glu Glu
 3795 3800 3805
 Pro Glu Thr Gln Ala Val Leu Ser Asp Thr Glu Lys Ile Phe Pro Ser
 3810 3815 3820
 Ala Met Ser Ile Glu Gln Ile Asn Ser Leu Thr Val Glu Pro Leu Lys
 3825 3830 3835 3840
 Thr Leu Leu Ala Glu Pro Glu Gly Asn Tyr Pro Gln Ser Ser Ile Glu
 3845 3850 3855
 Pro Pro Met His Ser Tyr Leu Thr Ser Val Ala Glu Glu Val Leu Ser
 3860 3865 3870
 Leu Lys Glu Lys Thr Val Ser Asp Thr Asn Arg Glu Gln Arg Val Thr
 3875 3880 3885
 Leu Gln Lys Gln Glu Ala Gln Ser Ala Leu Ile Leu Ser Gln Ser Leu
 3890 3895 3900
 Ala Glu Gly His Val Glu Ser Leu Gln Ser Pro Asp Val Met Ile Ser
 3905 3910 3915 3920
 Gln Val Asn Tyr Glu Pro Leu Val Pro Ser Glu His Ser Cys Thr Glu
 3925 3930 3935
 Gly Gly Lys Ile Leu Ile Glu Ser Ala Asn Pro Leu Glu Asn Ala Gly
 3940 3945 3950
 Gln Asp Ser Ala Val Arg Ile Glu Glu Gly Lys Ser Leu Arg Phe Pro
 3955 3960 3965
 Leu Ala Leu Glu Glu Lys Gln Val Leu Leu Lys Glu Glu His Ser Asp
 3970 3975 3980
 Asn Val Val Met Pro Pro Asp Gln Ile Ile Glu Ser Lys Arg Glu Pro
 3985 3990 3995 4000
 Val Ala Ile Lys Lys Val Gln Glu Val Gln Gly Arg Asp Leu Leu Ser
 4005 4010 4015
 Lys Glu Ser Leu Leu Ser Gly Ile Pro Glu Glu Gln Arg Leu Asn Leu
 4020 4025 4030
 Lys Ile Gln Ile Cys Arg Ala Leu Gln Ala Ala Val Ala Ser Glu Gln
 4035 4040 4045
 Pro Gly Leu Phe Ser Glu Trp Leu Arg Asn Ile Glu Lys Val Glu Val
 4050 4055 4060
 Glu Ala Val Asn Ile Thr Gln Glu Pro Arg His Ile Met Cys Met Tyr
 4065 4070 4075 4080
 Leu Val Thr Ser Ala Lys Ser Val Thr Glu Glu Val Thr Ile Ile Ile
 4085 4090 4095
 Glu Asp Val Asp Pro Gln Met Ala Asn Leu Lys Met Glu Leu Arg Asp
 4100 4105 4110
 Ala Leu Cys Ala Ile Ile Tyr Glu Glu Ile Asp Ile Leu Thr Ala Glu
 4115 4120 4125
 Gly Pro Arg Ile Gln Gln Gly Ala Lys Thr Ser Leu Gln Glu Glu Met
 4130 4135 4140
 Asp Ser Phe Ser Gly Ser Gln Lys Val Glu Pro Ile Thr Glu Pro Glu
 4145 4150 4155 4160
 Val Glu Ser Lys Tyr Leu Ile Ser Thr Glu Glu Val Ser Tyr Phe Asn
 4165 4170 4175
 Val Gln Ser Arg Val Lys Tyr Leu Asp Ala Thr Pro Val Thr Lys Gly
 4180 4185 4190

Val Ala Ser Ala Val Val Ser Asp Glu Lys Gln Asp Glu Ser Leu Lys
 4195 4200 4205
 Pro Ser Glu Glu Lys Glu Glu Ser Ser Glu Ser Gly Thr Glu Glu
 4210 4215 4220
 Val Ala Thr Val Lys Ile Gln Glu Ala Glu Gly Gly Leu Ile Lys Glu
 4225 4230 4235 4240
 Asp Gly Pro Met Ile His Thr Pro Leu Val Asp Thr Val Ser Glu Glu
 4245 4250 4255
 Gly Asp Ile Val His Leu Thr Thr Ser Ile Thr Asn Ala Lys Glu Val
 4260 4265 4270
 Asn Trp Tyr Phe Glu Asn Lys Leu Val Pro Ser Asp Glu Lys Phe Lys
 4275 4280 4285
 Cys Leu Gln Asp Gln Asn Thr Tyr Thr Leu Val Ile Asp Lys Val Asn
 4290 4295 4300
 Thr Glu Asp His Gln Gly Glu Tyr Val Cys Glu Ala Leu Asn Asp Ser
 4305 4310 4315 4320
 Gly Lys Thr Ala Thr Ser Ala Lys Leu Thr Val Val Lys Arg Ala Ala
 4325 4330 4335
 Pro Val Ile Lys Arg Lys Ile Glu Pro Leu Glu Val Ala Leu Gly His
 4340 4345 4350
 Leu Ala Lys Phe Thr Cys Glu Ile Gln Ser Ala Pro Asn Val Arg Phe
 4355 4360 4365
 Gln Trp Phe Lys Ala Gly Arg Glu Ile Tyr Glu Ser Asp Lys Cys Ser
 4370 4375 4380
 Ile Arg Ser Ser Lys Tyr Ile Ser Ser Leu Glu Ile Leu Arg Thr Gln
 4385 4390 4395 4400
 Val Val Asp Cys Gly Glu Tyr Thr Cys Lys Ala Ser Asn Glu Tyr Gly
 4405 4410 4415
 Ser Val Ser Cys Thr Ala Thr Leu Thr Val Thr Val Pro Gly Gly Glu
 4420 4425 4430
 Lys Lys Val Arg Lys Leu Leu Pro Glu Arg Lys Pro Glu Pro Lys Glu
 4435 4440 4445
 Glu Val Val Leu Lys Ser Val Leu Arg Lys Arg Pro Glu Glu Glu Glu
 4450 4455 4460
 Pro Lys Val Glu Pro Lys Lys Leu Glu Lys Val Lys Lys Pro Ala Val
 4465 4470 4475 4480
 Pro Glu Pro Pro Pro Lys Pro Val Glu Glu Val Glu Val Pro Thr
 4485 4490 4495
 Val Thr Lys Arg Glu Arg Lys Ile Pro Glu Pro Thr Lys Val Pro Glu
 4500 4505 4510
 Ile Lys Pro Ala Ile Pro Leu Pro Ala Pro Glu Pro Lys Pro Lys Pro
 4515 4520 4525
 Glu Ala Glu Val Lys Thr Ile Lys Pro Pro Pro Val Glu Pro Glu Pro
 4530 4535 4540
 Thr Pro Ile Ala Ala Pro Val Thr Val Pro Val Val Gly Lys Lys Ala
 4545 4550 4555 4560
 Glu Ala Lys Ala Pro Lys Glu Glu Ala Ala Lys Pro Lys Gly Pro Ile
 4565 4570 4575
 Lys Gly Val Pro Lys Lys Thr Pro Ser Pro Ile Glu Ala Glu Arg Arg
 4580 4585 4590
 Lys Leu Arg Pro Gly Ser Gly Gly Glu Lys Pro Pro Asp Glu Ala Pro
 4595 4600 4605
 Phe Thr Tyr Gln Leu Lys Ala Val Pro Leu Lys Phe Val Lys Glu Ile
 4610 4615 4620
 Lys Asp Ile Ile Leu Thr Glu Ser Glu Phe Val Gly Ser Ser Ala Ile
 4625 4630 4635 4640
 Phe Glu Cys Leu Val Ser Pro Ser Thr Ala Ile Thr Thr Trp Met Lys
 4645 4650 4655
 Asp Gly Ser Asn Ile Arg Glu Ser Pro Lys His Arg Phe Ile Ala Asp
 4660 4665 4670
 Gly Lys Asp Arg Lys Leu His Ile Ile Asp Val Gln Leu Ser Asp Ala
 4675 4680 4685

Gly Glu Tyr Thr Cys Val Leu Arg Leu Gly Asn Lys Glu Lys Thr Ser
 4690 4695 4700
 Thr Ala Lys Leu Val Val Glu Glu Leu Pro Val Arg Phe Val Lys Thr
 4705 4710 4715 4720
 Leu Glu Glu Glu Val Thr Val Val Lys Gly Gln Pro Leu Tyr Leu Ser
 4725 4730 4735
 Cys Glu Leu Asn Lys Glu Arg Asp Val Val Trp Arg Lys Asp Gly Lys
 4740 4745 4750
 Ile Val Val Glu Lys Pro Gly Arg Ile Val Pro Gly Val Ile Gly Leu
 4755 4760 4765
 Met Arg Ala Leu Thr Ile Asn Asp Ala Asp Asp Thr Asp Ala Gly Thr
 4770 4775 4780
 Tyr Thr Val Thr Val Glu Asn Ala Asn Asn Leu Glu Cys Ser Ser Cys
 4785 4790 4795 4800
 Val Lys Val Val Glu Val Ile Arg Asp Trp Leu Val Lys Pro Ile Arg
 4805 4810 4815
 Asp Gln His Val Lys Pro Lys Gly Thr Ala Ile Phe Ala Cys Asp Ile
 4820 4825 4830
 Ala Lys Asp Thr Pro Asn Ile Lys Trp Phe Lys Gly Tyr Asp Glu Ile
 4835 4840 4845
 Pro Ala Glu Pro Asn Asp Lys Thr Glu Ile Leu Arg Asp Gly Asn His
 4850 4855 4860
 Leu Tyr Leu Lys Ile Lys Asn Ala Met Pro Glu Asp Ile Ala Glu Tyr
 4865 4870 4875 4880
 Ala Val Glu Ile Glu Gly Lys Arg Tyr Pro Ala Lys Leu Thr Leu Gly
 4885 4890 4895
 Glu Arg Glu Val Glu Leu Leu Lys Pro Ile Glu Asp Val Thr Ile Tyr
 4900 4905 4910
 Glu Lys Glu Ser Ala Ser Phe Asp Ala Glu Ile Ser Glu Ala Asp Ile
 4915 4920 4925
 Pro Gly Gln Trp Lys Leu Lys Gly Glu Leu Leu Arg Pro Ser Pro Thr
 4930 4935 4940
 Cys Glu Ile Lys Ala Glu Gly Gly Lys Arg Phe Leu Thr Leu His Lys
 4945 4950 4955 4960
 Val Lys Leu Asp Gln Ala Gly Glu Val Leu Tyr Gln Ala Leu Asn Ala
 4965 4970 4975
 Ile Thr Thr Ala Ile Leu Thr Val Lys Glu Ile Glu Leu Asp Phe Ala
 4980 4985 4990
 Val Pro Leu Lys Asp Val Thr Val Pro Glu Arg Arg Gln Ala Arg Phe
 4995 5000 5005
 Glu Cys Val Leu Thr Arg Glu Ala Asn Val Ile Trp Ser Lys Gly Pro
 5010 5015 5020
 Asp Ile Ile Lys Ser Ser Asp Lys Phe Asp Ile Ile Ala Asp Gly Lys
 5025 5030 5035 5040
 Lys His Ile Leu Val Ile Asn Asp Ser Gln Phe Asp Asp Glu Gly Val
 5045 5050 5055
 Tyr Thr Ala Glu Val Glu Gly Lys Lys Thr Ser Ala Arg Leu Phe Val
 5060 5065 5070
 Thr Gly Ile Arg Leu Lys Phe Met Ser Pro Leu Glu Asp Gln Thr Val
 5075 5080 5085
 Lys Glu Gly Glu Thr Ala Thr Phe Val Cys Glu Leu Ser His Glu Lys
 5090 5095 5100
 Met His Val Val Trp Phe Lys Asn Asp Ala Lys Leu His Thr Ser Arg
 5105 5110 5115 5120
 Thr Val Leu Ile Ser Ser Glu Gly Lys Thr His Lys Leu Glu Met Lys
 5125 5130 5135
 Glu Val Thr Leu Asp Asp Ile Ser Gln Ile Lys Ala Gln Val Lys Glu
 5140 5145 5150
 Leu Ser Ser Thr Ala Gln Leu Lys Val Leu Glu Ala Asp Pro Tyr Phe
 5155 5160 5165
 Thr Val Lys Leu His Asp Lys Thr Ala Val Glu Lys Asp Glu Ile Thr
 5170 5175 5180

Leu Lys Cys Glu Val Ser Lys Asp Val Pro Val Lys Trp Phe Lys Asp
 5185 5190 5195 5200
 Gly Glu Glu Ile Val Pro Ser Pro Lys Tyr Ser Ile Lys Ala Asp Gly
 5205 5210 5215
 Leu Arg Arg Ile Leu Lys Ile Lys Lys Ala Asp Leu Lys Asp Lys Gly
 5220 5225 5230
 Glu Tyr Val Cys Asp Cys Gly Thr Asp Lys Thr Lys Ala Asn Val Thr
 5235 5240 5245
 Val Glu Ala Arg Leu Ile Glu Val Glu Lys Pro Leu Tyr Gly Val Glu
 5250 5255 5260
 Val Phe Val Gly Glu Thr Ala His Phe Glu Ile Glu Leu Ser Glu Pro
 5265 5270 5275 5280
 Asp Val His Gly Gln Trp Lys Leu Lys Gly Gln Pro Leu Thr Ala Ser
 5285 5290 5295
 Pro Asp Cys Glu Ile Ile Glu Asp Gly Lys Lys His Ile Leu Ile Leu
 5300 5305 5310
 His Asn Cys Gln Leu Gly Met Thr Gly Glu Val Ser Phe Gln Ala Ala
 5315 5320 5325
 Asn Ala Lys Ser Ala Ala Asn Leu Lys Val Lys Glu Leu Pro Leu Ile
 5330 5335 5340
 Phe Ile Thr Pro Leu Ser Asp Val Lys Val Phe Glu Lys Asp Glu Ala
 5345 5350 5355 5360
 Lys Phe Glu Cys Glu Val Ser Arg Glu Pro Lys Thr Phe Arg Trp Leu
 5365 5370 5375
 Lys Gly Thr Gln Glu Ile Thr Gly Asp Asp Arg Phe Glu Leu Ile Lys
 5380 5385 5390
 Asp Gly Thr Lys His Ser Met Val Ile Lys Ser Ala Ala Phe Glu Asp
 5395 5400 5405
 Glu Ala Lys Tyr Met Phe Glu Ala Glu Asp Lys His Thr Ser Gly Lys
 5410 5415 5420
 Leu Ile Ile Glu Gly Ile Arg Leu Lys Phe Leu Thr Pro Leu Lys Asp
 5425 5430 5435 5440
 Val Thr Ala Lys Glu Lys Glu Ser Ala Val Phe Thr Val Glu Leu Ser
 5445 5450 5455
 His Asp Asn Ile Arg Val Lys Trp Phe Lys Asn Asp Gln Arg Leu His
 5460 5465 5470
 Thr Thr Arg Ser Val Ser Met Gln Asp Glu Gly Lys Thr His Ser Ile
 5475 5480 5485
 Thr Phe Lys Asp Leu Ser Ile Asp Asp Thr Ser Gln Ile Arg Val Glu
 5490 5495 5500
 Ala Met Gly Met Ser Ser Glu Ala Lys Leu Thr Val Leu Glu Gly Asp
 5505 5510 5515 5520
 Pro Tyr Phe Thr Gly Lys Leu Gln Asp Tyr Thr Gly Val Glu Lys Asp
 5525 5530 5535
 Glu Val Ile Leu Gln Cys Glu Ile Ser Lys Ala Asp Ala Pro Val Lys
 5540 5545 5550
 Trp Phe Lys Asp Gly Lys Glu Ile Lys Pro Ser Lys Asn Ala Val Ile
 5555 5560 5565
 Lys Thr Asp Gly Lys Lys Arg Met Leu Ile Leu Lys Lys Ala Leu Lys
 5570 5575 5580
 Ser Asp Ile Gly Gln Tyr Thr Cys Asp Cys Gly Thr Asp Lys Thr Ser
 5585 5590 5595 5600
 Gly Lys Leu Asp Ile Glu Asp Arg Glu Ile Lys Leu Val Arg Pro Leu
 5605 5610 5615
 His Ser Val Glu Val Met Glu Thr Glu Thr Ala Arg Phe Glu Thr Glu
 5620 5625 5630
 Ile Ser Glu Asp Asp Ile His Ala Asn Trp Lys Leu Lys Gly Glu Ala
 5635 5640 5645
 Leu Leu Gln Thr Pro Asp Cys Glu Ile Lys Glu Glu Gly Lys Ile His
 5650 5655 5660
 Ser Leu Val Leu His Asn Cys Arg Leu Asp Gln Thr Gly Gly Val Asp
 5665 5670 5675 5680

Phe Gln Ala Ala Asn Val Lys Ser Ser Ala His Leu Arg Val Lys Pro
 5685 5690 5695
 Arg Val Ile Gly Leu Leu Arg Pro Leu Lys Asp Val Thr Val Thr Ala
 5700 5705 5710
 Gly Glu Thr Ala Thr Phe Asp Cys Glu Leu Ser Tyr Glu Asp Ile Pro
 5715 5720 5725
 Val Glu Trp Tyr Leu Lys Gly Lys Lys Leu Glu Pro Ser Asp Lys Val
 5730 5735 5740
 Val Pro Arg Ser Glu Gly Lys Val His Thr Leu Thr Leu Arg Asp Val
 5745 5750 5755 5760
 Lys Leu Glu Asp Ala Gly Glu Val Gln Leu Thr Ala Lys Asp Phe Lys
 5765 5770 5775
 Thr His Ala Asn Leu Phe Val Lys Glu Pro Pro Val Glu Phe Thr Lys
 5780 5785 5790
 Pro Leu Glu Asp Gln Thr Val Glu Glu Gly Ala Thr Ala Val Leu Glu
 5795 5800 5805
 Cys Glu Val Ser Arg Glu Asn Ala Lys Val Lys Trp Phe Lys Asn Gly
 5810 5815 5820
 Thr Glu Ile Leu Lys Ser Lys Lys Tyr Glu Ile Val Ala Asp Gly Arg
 5825 5830 5835 5840
 Val Arg Lys Leu Val Ile His Asp Cys Thr Pro Glu Asp Ile Lys Thr
 5845 5850 5855
 Tyr Thr Cys Asp Ala Lys Asp Phe Lys Thr Ser Cys Asn Leu Asn Val
 5860 5865 5870
 Val Pro Pro His Val Glu Phe Leu Arg Pro Leu Thr Asp Leu Gln Val
 5875 5880 5885
 Arg Glu Lys Glu Met Ala Arg Phe Glu Cys Glu Leu Ser Arg Glu Asn
 5890 5895 5900
 Ala Lys Val Lys Trp Phe Lys Asp Gly Ala Glu Ile Lys Lys Gly Lys
 5905 5910 5915 5920
 Lys Tyr Asp Ile Ile Ser Lys Gly Ala Val Arg Ile Leu Val Ile Asn
 5925 5930 5935
 Lys Cys Leu Leu Asp Asp Glu Ala Glu Tyr Ser Cys Glu Val Arg Thr
 5940 5945 5950
 Ala Arg Thr Ser Gly Met Leu Thr Val Leu Glu Glu Ala Val Phe
 5955 5960 5965
 Thr Lys Asn Leu Ala Asn Ile Glu Val Ser Glu Thr Asp Thr Ile Lys
 5970 5975 5980
 Leu Val Cys Glu Val Ser Lys Pro Gly Ala Glu Val Ile Trp Tyr Lys
 5985 5990 5995 6000
 Gly Asp Glu Glu Ile Ile Glu Thr Gly Arg Tyr Glu Ile Leu Thr Glu
 6005 6010 6015
 Gly Arg Lys Arg Ile Leu Val Ile Gln Asn Ala His Leu Glu Asp Ala
 6020 6025 6030
 Gly Asn Tyr Asn Cys Arg Leu Pro Ser Ser Arg Thr Asp Gly Lys Val
 6035 6040 6045
 Lys Val His Glu Leu Ala Ala Glu Phe Ile Ser Lys Pro Gln Asn Leu
 6050 6055 6060
 Glu Ile Leu Glu Gly Glu Lys Ala Glu Phe Val Cys Ser Ile Ser Lys
 6065 6070 6075 6080
 Glu Ser Phe Pro Val Gln Trp Lys Arg Asp Asp Lys Thr Leu Glu Ser
 6085 6090 6095
 Gly Asp Lys Tyr Asp Val Ile Ala Asp Gly Lys Lys Arg Val Leu Val
 6100 6105 6110
 Val Lys Asp Ala Thr Leu Gln Asp Met Gly Thr Tyr Val Val Met Val
 6115 6120 6125
 Gly Ala Ala Arg Ala Ala Ala His Leu Thr Val Ile Glu Lys Leu Arg
 6130 6135 6140
 Ile Val Val Pro Leu Lys Asp Thr Arg Val Lys Glu Gln Gln Glu Val
 6145 6150 6155 6160
 Val Phe Asn Cys Glu Val Asn Thr Glu Gly Ala Lys Ala Lys Trp Phe
 6165 6170 6175

Arg Asn Glu Glu Ala Ile Phe Asp Ser Ser Lys Tyr Ile Ile Leu Gln
 6180 6185 6190
 Lys Asp Leu Val Tyr Thr Leu Arg Ile Arg Asp Ala His Leu Asp Asp
 6195 6200 6205
 Gln Ala Asn Tyr Asn Val Ser Leu Thr Asn His Arg Gly Glu Asn Val
 6210 6215 6220
 Lys Ser Ala Ala Asn Leu Ile Val Glu Glu Glu Asp Leu Arg Ile Val
 6225 6230 6235 6240
 Glu Pro Leu Lys Asp Ile Glu Thr Met Glu Lys Lys Ser Val Thr Phe
 6245 6250 6255
 Trp Cys Lys Val Asn Arg Leu Asn Val Thr Lys Lys Trp Thr Lys Asn
 6260 6265 6270
 Gly Glu Glu Val Pro Phe Asp Asn Arg Val Ser Tyr Arg Val Asp Lys
 6275 6280 6285
 Tyr Lys His Met Leu Thr Ile Lys Asp Cys Gly Phe Pro Asp Glu Gly
 6290 6295 6300
 Glu Tyr Ile Val Thr Ala Gly Gln Asp Lys Ser Val Ala Glu Leu Leu
 6305 6310 6315 6320
 Ile Ile Glu Ala Pro Thr Glu Phe Val Glu His Leu Glu Asp Gln Thr
 6325 6330 6335
 Val Thr Glu Phe Asp Asp Ala Val Phe Ser Cys Gln Leu Ser Arg Glu
 6340 6345 6350
 Lys Ala Asn Val Lys Trp Tyr Arg Asn Gly Arg Glu Ile Lys Glu Gly
 6355 6360 6365
 Lys Lys Tyr Lys Phe Glu Lys Asp Gly Ser Ile His Arg Leu Ile Ile
 6370 6375 6380
 Lys Asp Cys Arg Leu Asp Asp Glu Cys Glu Tyr Ala Cys Gly Val Glu
 6385 6390 6395 6400
 Asp Arg Lys Ser Arg Ala Arg Leu Phe Val Glu Glu Ile Pro Val Glu
 6405 6410 6415
 Ile Ile Arg Pro Pro Gln Asp Ile Leu Glu Ala Pro Gly Ala Asp Val
 6420 6425 6430
 Val Phe Leu Ala Glu Leu Asn Lys Asp Lys Val Glu Val Gln Trp Leu
 6435 6440 6445
 Arg Asn Asn Met Val Val Val Gln Gly Asp Lys His Gln Met Met Ser
 6450 6455 6460
 Glu Gly Lys Ile His Arg Leu Gln Ile Cys Asp Ile Lys Pro Arg Asp
 6465 6470 6475 6480
 Gln Gly Glu Tyr Arg Phe Ile Ala Lys Asp Lys Glu Ala Arg Ala Lys
 6485 6490 6495
 Leu Glu Leu Ala Ala Pro Lys Ile Lys Thr Ala Asp Gln Asp Leu
 6500 6505 6510
 Val Val Asp Val Gly Lys Pro Leu Thr Met Val Val Pro Tyr Asp Ala
 6515 6520 6525
 Tyr Pro Lys Ala Glu Ala Glu Trp Phe Lys Glu Asn Glu Pro Leu Ser
 6530 6535 6540
 Thr Lys Thr Ile Asp Thr Thr Ala Glu Gln Thr Ser Phe Arg Ile Leu
 6545 6550 6555 6560
 Glu Ala Lys Lys Gly Asp Lys Gly Arg Tyr Lys Ile Val Leu Gln Asn
 6565 6570 6575
 Lys His Gly Lys Ala Glu Gly Phe Ile Asn Leu Lys Val Ile Asp Val
 6580 6585 6590
 Pro Gly Pro Val Arg Asn Leu Glu Val Thr Glu Thr Phe Asp Gly Glu
 6595 6600 6605
 Val Ser Leu Ala Trp Glu Glu Pro Leu Thr Asp Gly Gly Ser Lys Ile
 6610 6615 6620
 Ile Gly Tyr Val Val Glu Arg Arg Asp Ile Lys Arg Lys Thr Trp Val
 6625 6630 6635 6640
 Leu Ala Thr Asp Arg Ala Glu Ser Cys Glu Phe Thr Val Thr Gly Leu
 6645 6650 6655
 Gln Lys Gly Gly Val Glu Tyr Leu Phe Arg Val Ser Ala Arg Asn Arg
 6660 6665 6670

Val Gly Thr Gly Glu Pro Val Glu Thr Asp Asn Pro Val Glu Ala Arg
 6675 6680 6685
 Ser Lys Tyr Asp Val Pro Gly Pro Pro Leu Asn Val Thr Ile Thr Asp
 6690 6695 6700
 Val Asn Arg Phe Gly Val Ser Leu Thr Trp Glu Pro Pro Glu Tyr Asp
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 Gly Gly Ala Glu Ile Thr Asn Tyr Val Ile Glu Leu Arg Asp Lys Thr
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 Ser Ile Arg Trp Asp Thr Ala Met Thr Val Arg Ala Glu Asp Leu Ser
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 Leu Thr Ser Ser Asp Gln Thr Gln Ser Ser Val Gln Leu Lys Trp Glu
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 Pro Pro Leu Lys Asp Gly Gly Ser Pro Ile Leu Gly Tyr Ile Ile Glu
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 Arg Cys Glu Glu Gly Lys Asp Asn Trp Ile Arg Cys Asn Met Lys Leu
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 Val Pro Glu Leu Thr Tyr Lys Val Thr Gly Leu Glu Lys Gly Asn Lys
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 Tyr Leu Tyr Arg Val Ser Ala Glu Asn Lys Ala Gly Val Ser Asp Pro
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 Glu Arg Ser Asp Lys Gly Ile Tyr Thr Leu Lys Leu Glu Asn Arg Val
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 Lys Thr Ile Ser Gly Glu Ile Asp Val Asn Val Ile Ala Arg Pro Ser
 6980 6985 6990
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 Leu Thr Trp Glu Pro Pro Asp Asp Asp Gly Gly Ser Pro Leu Thr Gly
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 Tyr Val Val Glu Lys Arg Glu Val Ser Arg Lys Thr Trp Thr Lys Val
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 Gly Lys Glu Tyr Leu Phe Lys Val Cys Ala Arg Asn Lys Cys Gly Pro
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 Gly Glu Pro Ala Tyr Val Asp Glu Pro Val Asn Met Ser Thr Pro Ala
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 Thr Val Pro Asp Pro Pro Glu Asn Val Lys Trp Arg Asp Arg Thr Ala
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 Asn Ser Ile Phe Leu Thr Trp Asp Pro Pro Lys Asn Asp Gly Gly Ser
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 Arg Ile Lys Gly Tyr Ile Val Glu Arg Cys Pro Arg Gly Ser Asp Lys
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 Trp Val Ala Cys Gly Glu Pro Val Ala Glu Thr Lys Met Glu Val Thr
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 Gly Leu Glu Glu Gly Lys Trp Tyr Ala Tyr Arg Val Lys Thr Leu Asn
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Arg Gln Gly Ala Ser Lys Pro Ser Arg Pro Thr Glu Glu Ile Gln Ala
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 Val Asp Thr Gln Glu Ala Pro Glu Ile Phe Leu Asp Val Lys Leu Leu
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 Ala Gly Leu Thr Val Lys Ala Gly Thr Lys Ile Glu Leu Pro Ala Thr
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 Val Thr Gly Lys Pro Glu Pro Lys Ile Thr Trp Thr Lys Ala Asp Met
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 Ile Leu Lys Gln Asp Lys Arg Ile Thr Ile Glu Asn Val Pro Lys Lys
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 Ser Thr Val Thr Ile Val Asp Ser Lys Arg Ser Asp Thr Gly Thr Tyr
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 Ile Ile Glu Ala Val Asn Val Cys Gly Arg Ala Thr Ala Val Val Glu
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 Val Asn Val Leu Asp Lys Pro Gly Pro Ala Ala Phe Asp Ile Thr
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 Asp Val Thr Asn Glu Ser Cys Leu Thr Trp Asn Pro Pro Arg Asp
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 Ile Thr Ala Lys Tyr Gln Phe Asp Pro Pro Gly Pro Pro Thr Arg Leu
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 Glu Pro Ser Asp Ile Thr Lys Asp Ala Val Thr Leu Thr Trp Cys Glu
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 Pro Asp Asp Asp Gly Gly Ser Pro Ile Thr Gly Tyr Trp Val Glu Arg
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 Leu Asp Pro Asp Thr Asp Lys Trp Val Arg Cys Asn Lys Met Pro Val
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 Lys Asp Thr Thr Tyr Arg Val Lys Gly Leu Thr Asn Lys Lys Lys Tyr
 7445 7450 7455
 Arg Phe Arg Val Leu Ala Glu Asn Leu Ala Gly Pro Gly Lys Pro Ser
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 Lys Ser Thr Glu Pro Ile Leu Ile Lys Asp Pro Ile Asp Pro Pro Trp
 7475 7480 7485
 Pro Pro Gly Lys Pro Thr Val Lys Asp Val Gly Lys Thr Ser Val Arg
 7490 7495 7500
 Leu Asn Trp Thr Lys Pro Glu His Asp Gly Gly Ala Lys Ile Glu Ser
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 Tyr Val Ile Glu Met Leu Lys Thr Gly Thr Asp Glu Trp Val Arg Val
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 Ala Glu Gly Val Pro Thr Thr Gln His Leu Leu Pro Gly Leu Met Glu
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 Gly Gln Glu Tyr Ser Phe Arg Val Arg Ala Val Asn Lys Ala Gly Glu
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 Ser Glu Pro Ser Glu Pro Ser Asp Pro Val Leu Cys Arg Glu Lys Leu
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 Tyr Pro Pro Ser Pro Pro Arg Trp Leu Glu Val Ile Asn Ile Thr Lys
 7585 7590 7595 7600
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 Pro Ile Thr Asn Tyr Ile Val Glu Lys Arg Asp Val Arg Arg Lys Gly
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 Trp Gln Thr Val Asp Thr Thr Val Lys Asp Thr Lys Cys Thr Val Thr
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 Pro Leu Thr Glu Gly Ser Leu Tyr Val Phe Arg Val Ala Ala Glu Asn
 7650 7655 7660

Ala Ile Gly Gln Ser Asp Tyr Thr Glu Ile Glu Asp Ser Val Leu Ala
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 Lys Asp Thr Phe Thr Thr Pro Gly Pro Pro Tyr Ala Leu Ala Val Val
 7685 7690 7695
 Asp Val Thr Lys Arg His Val Asp Leu Lys Trp Glu Pro Pro Lys Asn
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 Asp Gly Gly Arg Pro Ile Gln Arg Tyr Val Ile Glu Lys Lys Glu Arg
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 Leu Gly Thr Arg Trp Val Lys Ala Gly Lys Thr Ala Gly Pro Asp Cys
 7730 7735 7740
 Asn Phe Arg Val Thr Asp Val Ile Glu Gly Thr Glu Val Gln Phe Gln
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 Val Arg Ala Glu Asn Glu Ala Gly Val Gly His Pro Ser Glu Pro Thr
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 Glu Ile Leu Ser Ile Glu Asp Pro Thr Ser Pro Pro Ser Pro Leu
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 Asp Leu His Val Thr Asp Ala Gly Arg Lys His Ile Ala Ile Ala Trp
 7795 7800 7805
 Lys Pro Pro Glu Lys Asn Gly Gly Ser Pro Ile Ile Gly Tyr His Val
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 Glu Met Cys Pro Val Gly Thr Glu Lys Trp Met Arg Val Asn Ser Arg
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 Pro Ile Lys Asp Leu Lys Phe Lys Val Glu Glu Gly Val Val Pro Asp
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 Lys Glu Tyr Val Leu Arg Val Arg Ala Val Asn Ala Ile Gly Val Ser
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 Glu Pro Ser Glu Ile Ser Glu Asn Val Val Ala Lys Asp Pro Asp Cys
 7875 7880 7885
 Lys Pro Thr Ile Asp Leu Glu Thr His Asp Ile Ile Val Ile Glu Gly
 7890 7895 7900
 Glu Lys Leu Ser Ile Pro Val Pro Phe Arg Ala Val Pro Val Pro Thr
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 Val Ser Trp His Lys Asp Gly Lys Glu Val Lys Ala Ser Asp Arg Leu
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 Thr Met Lys Asn Asp His Ile Ser Ala His Leu Glu Val Pro Lys Ser
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 Val Arg Ala Asp Ala Gly Ile Tyr Thr Ile Thr Leu Glu Asn Lys Leu
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 Gly Ser Ala Thr Ala Ser Ile Asn Val Lys Val Ile Gly Leu Pro Gly
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 Pro Cys Lys Asp Ile Lys Ala Ser Asp Ile Thr Lys Ser Ser Cys Lys
 7985 7990 7995 8000
 Leu Thr Trp Glu Pro Pro Glu Phe Asp Gly Gly Thr Pro Ile Leu His
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 Tyr Val Leu Glu Arg Arg Glu Ala Gly Arg Arg Thr Tyr Ile Pro Val
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 Asn Gly Glu Tyr Phe Phe Arg Val Lys Ala Val Asn Lys Val Gly Gly
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 Gly Glu Tyr Ile Glu Leu Lys Asn Pro Val Ile Ala Gln Asp Pro Lys
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 Gln Pro Pro Asp Pro Pro Val Asp Val Glu Val His Asn Pro Thr Ala
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 Glu Ala Met Thr Ile Thr Trp Lys Pro Pro Leu Tyr Asp Gly Gly Ser
 8100 8105 8110
 Lys Ile Met Gly Tyr Ile Ile Glu Lys Ile Ala Lys Gly Glu Glu Arg
 8115 8120 8125
 Trp Lys Arg Cys Asn Glu His Leu Val Pro Ile Leu Thr Tyr Thr Ala
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 Lys Gly Leu Glu Glu Gly Lys Glu Tyr Gln Phe Arg Val Arg Ala Glu
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Asn Ala Ala Gly Ile Ser Glu Pro Ser Arg Ala Thr Pro Pro Thr Lys
 8165 8170 8175
 Ala Val Asp Pro Ile Asp Ala Pro Lys Val Ile Leu Arg Thr Ser Leu
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 Glu Val Lys Arg Gly Asp Glu Ile Ala Leu Asp Ala Ser Ile Ser Gly
 8195 8200 8205
 Ser Pro Tyr Pro Thr Ile Thr Trp Ile Lys Asp Glu Asn Val Ile Val
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 Pro Glu Glu Ile Lys Lys Arg Ala Ala Pro Leu Val Arg Arg Arg Lys
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 Gly Glu Val Gln Glu Glu Glu Pro Phe Val Leu Pro Leu Thr Gln Arg
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 Leu Ser Ile Asp Asn Ser Lys Lys Gly Glu Ser Gln Leu Arg Val Arg
 8260 8265 8270
 Asp Ser Leu Arg Pro Asp His Gly Leu Tyr Met Ile Lys Val Glu Asn
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 Asp His Gly Ile Ala Lys Ala Pro Cys Thr Val Ser Val Leu Asp Thr
 8290 8295 8300
 Pro Gly Pro Pro Ile Asn Phe Val Phe Glu Asp Ile Arg Lys Thr Ser
 8305 8310 8315 8320
 Val Leu Cys Lys Trp Glu Pro Pro Leu Asp Asp Gly Gly Ser Glu Ile
 8325 8330 8335
 Ile Asn Tyr Thr Leu Glu Lys Lys Asp Lys Thr Lys Pro Asp Ser Glu
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 Trp Ile Val Val Thr Ser Thr Leu Arg His Cys Lys Tyr Ser Val Thr
 8355 8360 8365
 Lys Leu Ile Glu Gly Lys Glu Tyr Leu Phe Arg Val Arg Ala Glu Asn
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 Arg Phe Gly Pro Gly Pro Pro Cys Val Ser Lys Pro Leu Val Ala Lys
 8385 8390 8395 8400
 Asp Pro Phe Gly Pro Pro Asp Ala Pro Asp Lys Pro Ile Val Glu Asp
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 Val Thr Ser Asn Ser Met Leu Val Lys Trp Asn Glu Pro Lys Asp Asn
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 Gly Ser Pro Ile Leu Gly Tyr Trp Leu Glu Lys Arg Glu Val Asn Ser
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 Thr His Trp Ser Arg Val Asn Lys Ser Leu Leu Asn Ala Leu Lys Ala
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 Asn Val Asp Gly Leu Leu Glu Gly Leu Thr Tyr Val Phe Arg Val Cys
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 Ala Glu Asn Ala Ala Gly Pro Gly Lys Phe Ser Pro Pro Ser Asp Pro
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 Lys Thr Ala His Asp Pro Ile Ser Pro Pro Gly Pro Pro Ile Pro Arg
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 Val Thr Asp Thr Ser Ser Thr Thr Ile Glu Leu Glu Trp Glu Pro Pro
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 Ala Phe Asn Gly Gly Gly Ile Val Gly Tyr Phe Val Asp Lys Gln
 8530 8535 8540
 Leu Val Gly Thr Asn Lys Trp Ser Arg Cys Thr Glu Lys Met Ile Lys
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 Val Arg Gln Tyr Thr Val Lys Glu Ile Arg Glu Gly Ala Asp Tyr Lys
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 Leu Arg Val Ser Ala Val Asn Ala Ala Gly Glu Gly Pro Pro Gly Glu
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 Thr Gln Pro Val Thr Val Ala Glu Pro Gln Glu Pro Pro Ala Val Glu
 8595 8600 8605
 Leu Asp Val Ser Val Lys Gly Gly Ile Gln Ile Met Ala Gly Lys Thr
 8610 8615 8620
 Leu Arg Ile Pro Ala Val Val Thr Gly Arg Pro Val Pro Thr Lys Val
 8625 8630 8635 8640
 Trp Thr Lys Glu Glu Gly Glu Leu Asp Lys Asp Arg Val Val Ile Asp
 8645 8650 8655

Asn Val Gly Thr Lys Ser Glu Leu Ile Ile Lys Asp Ala Leu Arg Lys
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 Asp His Gly Arg Tyr Val Ile Thr Ala Thr Asn Ser Cys Gly Ser Lys
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 Phe Ala Ala Ala Arg Val Glu Val Phe Asp Val Pro Gly Pro Val Leu
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 Asp Leu Lys Pro Val Val Thr Asn Arg Lys Met Cys Leu Leu Asn Trp
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 Ser Asp Pro Glu Asp Asp Gly Gly Ser Glu Ile Thr Gly Phe Ile Ile
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 Glu Arg Lys Asp Ala Lys Met His Thr Trp Arg Gln Pro Ile Glu Thr
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 Glu Arg Ser Lys Cys Asp Ile Thr Gly Leu Leu Glu Gly Gln Glu Tyr
 8755 8760 8765
 Lys Phe Arg Val Ile Ala Lys Asn Lys Phe Gly Cys Gly Pro Pro Val
 8770 8775 8780
 Glu Ile Gly Pro Ile Leu Ala Val Asp Pro Leu Gly Pro Pro Thr Ser
 8785 8790 8795 8800
 Pro Glu Arg Leu Thr Tyr Thr Glu Arg Gln Arg Ser Thr Ile Thr Leu
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 Asp Trp Lys Glu Pro Arg Ser Asn Gly Gly Ser Pro Ile Gln Gly Tyr
 8820 8825 8830
 Ile Ile Glu Lys Arg Arg His Asp Lys Pro Asp Phe Glu Arg Val Asn
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 Lys Arg Leu Cys Pro Thr Thr Ser Phe Leu Val Glu Asn Leu Asp Glu
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 His Gln Met Tyr Glu Phe Arg Val Lys Ala Val Asn Glu Ile Gly Glu
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 Ser Glu Pro Ser Leu Pro Leu Asn Val Val Ile Gln Asp Asp Glu Val
 8885 8890 8895
 Pro Pro Thr Ile Lys Leu Arg Leu Ser Val Arg Gly Asp Thr Ile Lys
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 Val Lys Ala Gly Glu Pro Val His Ile Pro Ala Asp Val Thr Gly Leu
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 Pro Met Pro Lys Ile Glu Trp Ser Lys Asn Glu Thr Val Ile Glu Lys
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 Pro Thr Asp Ala Leu Gln Ile Thr Lys Glu Glu Val Ser Arg Ser Glu
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 Ala Lys Thr Glu Leu Ser Ile Pro Lys Ala Val Arg Glu Asp Lys Gly
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 Thr Tyr Thr Val Thr Ala Ser Asn Arg Leu Gly Ser Val Phe Arg Asn
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 Val His Val Glu Val Tyr Asp Arg Pro Ser Pro Arg Asn Leu Ala
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 Val Thr Asp Ile Lys Ala Glu Ser Cys Tyr Leu Thr Trp Asp Ala Pro
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 Leu Asp Asn Gly Gly Ser Glu Ile Thr His Tyr Val Ile Asp Lys Arg
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 Val Glu Lys Arg Tyr Gly Ile Trp Lys Leu Ile Pro Asn Gly Gln Tyr
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 Glu Phe Arg Val Arg Ala Val Asn Lys Tyr Gly Ile Ser Asp Glu Cys
 9075 9080 9085
 Lys Ser Asp Lys Val Val Ile Gln Asp Pro Tyr Arg Leu Pro Gly Pro
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 Pro Gly Lys Pro Lys Val Leu Ala Arg Thr Lys Gly Ser Met Leu Val
 9105 9110 9115 9120
 Ser Trp Thr Pro Pro Leu Asp Asn Gly Gly Ser Pro Ile Thr Gly Tyr
 9125 9130 9135
 Trp Leu Glu Lys Arg Glu Glu Gly Ser Pro Tyr Trp Ser Arg Val Ser
 9140 9145 9150

Arg Ala Pro Ile Thr Lys Val Gly Leu Lys Gly Val Glu Phe Asn Val
 9155 9160 9165
 Pro Arg Leu Leu Glu Gly Val Lys Tyr Gln Phe Arg Ala Met Ala Ile
 9170 9175 9180
 Asn Ala Ala Gly Ile Gly Pro Pro Ser Glu Pro Ser Asp Pro Glu Val
 9185 9190 9195 9200
 Ala Gly Asp Pro Ile Phe Pro Pro Gly Pro Pro Ser Cys Pro Glu Val
 9205 9210 9215
 Lys Asp Lys Thr Lys Ser Ser Ile Ser Leu Gly Trp Lys Pro Pro Ala
 9220 9225 9230
 Lys Asp Gly Gly Ser Pro Ile Lys Gly Tyr Ile Val Glu Met Gln Glu
 9235 9240 9245
 Glu Gly Thr Thr Asp Trp Lys Arg Val Asn Glu Pro Asp Lys Leu Ile
 9250 9255 9260
 Thr Thr Cys Glu Cys Val Val Pro Asn Leu Lys Glu Leu Arg Lys Tyr
 9265 9270 9275 9280
 Arg Phe Arg Val Lys Ala Val Asn Glu Ala Gly Glu Ser Glu Pro Ser
 9285 9290 9295
 Asp Thr Thr Gly Glu Ile Pro Ala Thr Asp Ile Gln Glu Glu Pro Glu
 9300 9305 9310
 Val Phe Ile Asp Ile Gly Ala Gln Asp Cys Leu Val Cys Lys Ala Gly
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 Ser Gln Ile Arg Ile Pro Ala Val Ile Lys Gly Arg Pro Thr Pro Lys
 9330 9335 9340
 Ser Ser Trp Glu Phe Asp Gly Lys Ala Lys Lys Ala Met Lys Asp Gly
 9345 9350 9355 9360
 Val His Asp Ile Pro Glu Asp Ala Gln Leu Glu Thr Ala Glu Asn Ser
 9365 9370 9375
 Ser Val Ile Ile Ile Pro Glu Cys Lys Arg Ser His Thr Gly Lys Tyr
 9380 9385 9390
 Ser Ile Thr Ala Lys Asn Lys Ala Gly Gln Lys Thr Ala Asn Cys Arg
 9395 9400 9405
 Val Lys Val Met Asp Val Pro Gly Pro Pro Lys Asp Leu Lys Val Ser
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 Asp Ile Thr Arg Gly Ser Cys Arg Leu Ser Trp Lys Met Pro Asp Asp
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 Asp Gly Gly Asp Arg Ile Lys Gly Tyr Val Ile Glu Lys Arg Thr Ile
 9445 9450 9455
 Asp Gly Lys Ala Trp Thr Lys Val Asn Pro Asp Cys Gly Ser Thr Thr
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 Phe Val Val Pro Asp Leu Leu Ser Glu Gln Gln Tyr Phe Phe Arg Val
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 Arg Ala Glu Asn Arg Phe Gly Ile Gly Pro Pro Val Glu Thr Ile Gln
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 Arg Thr Thr Ala Arg Asp Pro Ile Tyr Pro Pro Asp Pro Pro Ile Lys
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 Pro Pro Lys Asn Asp Gly Gly Ser Pro Val Thr His Tyr Ile Val Glu
 9540 9545 9550
 Cys Leu Ala Trp Asp Pro Thr Gly Thr Lys Lys Glu Ala Trp Arg Gln
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 Cys Asn Lys Arg Asp Val Glu Glu Leu Gln Phe Thr Val Glu Asp Leu
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 Val Glu Gly Gly Glu Tyr Glu Phe Arg Val Lys Ala Val Asn Ala Ala
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 Gly Val Ser Lys Pro Ser Ala Thr Val Gly Pro Cys Asp Cys Gln Arg
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 Pro Asp Met Pro Pro Ser Ile Asp Leu Lys Glu Phe Met Glu Val Glu
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 Glu Gly Thr Asn Val Asn Ile Val Ala Lys Ile Lys Gly Val Pro Phe
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Pro Thr Leu Thr Trp Phe Lys Ala Pro Pro Lys Lys Pro Asp Asn Lys
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 Glu Pro Val Leu Tyr Asp Thr His Val Asn Lys Leu Val Val Asp Asp
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 Thr Cys Thr Leu Val Ile Pro Gln Ser Arg Arg Ser Asp Thr Gly Leu
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 Tyr Thr Ile Thr Ala Val Asn Asn Leu Gly Thr Ala Ser Lys Glu Met
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 Arg Leu Asn Val Leu Gly Arg Pro Gly Pro Pro Val Gly Pro Ile Lys
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 Phe Glu Ser Val Ser Ala Asp Gln Met Thr Leu Ser Trp Phe Pro Pro
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 Lys Asp Asp Gly Gly Ser Lys Ile Thr Asn Tyr Val Ile Glu Lys Arg
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 Glu Trp Glu Lys Gly Lys Asp Lys Glu Val Arg Gly Thr Lys Leu Val
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 Val Thr Gly Leu Lys Glu Gly Ala Phe Tyr Lys Phe Arg Val Ser Ala
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 Val Asn Ile Ala Gly Ile Gly Glu Pro Gly Glu Val Thr Asp Val Ile
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 Glu Met Lys Asp Arg Leu Val Ser Pro Asp Leu Gln Leu Asp Ala Ser
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 Ala Tyr Val Ser Gly Lys Pro Pro Thr Val Thr Trp Asn Met Asn
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 Ser Leu Leu Ala Lys Asn Glu Ala Gly Glu Arg Lys Lys Thr Ile Ile
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 Val Asp Val Leu Asp Val Pro Gly Pro Val Gly Thr Pro Phe Leu Ala
 10115 10120 10125
 His Asn Leu Thr Asn Glu Ser Cys Lys Leu Thr Trp Phe Ser Pro Glu
 10130 10135 10140 1

Asp Asp Gly Gly Ser Pro Ile Thr Asn Tyr Val Ile Glu Lys Arg Glu
 0145 10150 10155 10160
 Ser Asp Arg Arg Ala Trp Thr Pro Val Thr Tyr Thr Val Thr Arg Gln
 10165 10170 10175
 Asn Ala Thr Val Gln Gly Leu Ile Gln Gly Lys Ala Tyr Phe Phe Arg
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 Ile Ala Ala Glu Asn Ser Ile Gly Met Gly Pro Phe Val Glu Thr Ser
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 Glu Ala Leu Val Ile Arg Glu Pro Ile Thr Val Pro Glu Arg Pro Glu
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 Asp Leu Glu Val Lys Glu Val Thr Lys Asn Thr Val Thr Leu Thr Trp
 0225 10230 10235 10240
 Asn Pro Pro Lys Tyr Asp Gly Gly Ser Glu Ile Ile Asn Tyr Val Leu
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 Glu Ser Arg Leu Ile Gly Thr Glu Lys Phe His Lys Val Thr Asn Asp
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 Thr Tyr Glu Tyr Arg Val Ser Ala Val Asn Ile Val Gly Gln Gly Lys
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 Pro Ser Phe Cys Thr Lys Pro Ile Thr Cys Lys Asp Glu Leu Ala Pro
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 Pro Thr Leu His Leu Asp Phe Arg Asp Lys Leu Thr Ile Arg Val Gly
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 Glu Ala Phe Ala Leu Thr Gly Arg Tyr Ser Gly Lys Pro Lys Pro Lys
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 His Ile Lys Thr Thr Pro Ala Thr Leu Ala Leu Glu Lys Ile Lys Ala
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 Lys Arg Ser Asp Ser Gly Lys Tyr Cys Val Val Val Glu Asn Ser Thr
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 Pro Pro Val Gly Pro Val Ser Phe Asp Glu Val Thr Lys Asp Tyr Met
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 Val Ile Ser Trp Lys Pro Pro Leu Asp Asp Gly Gly Ser Lys Ile Thr
 10435 10440 10445
 Asn Tyr Ile Ile Glu Lys Lys Glu Val Gly Lys Asp Val Trp Met Pro
 10450 10455 10460 1
 Val Thr Ser Ala Ser Ala Lys Thr Thr Cys Lys Val Ser Lys Leu Leu
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 Glu Gly Lys Asp Tyr Ile Phe Arg Ile His Ala Glu Asn Leu Tyr Gly
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 Ile Ser Asp Pro Leu Val Ser Asp Ser Met Lys Ala Lys Asp Arg Phe
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 Ile Thr Asn Tyr Ile Leu Glu Lys Arg Glu Thr Met Ser Lys Arg Trp
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 Ala Arg Val Thr Lys Asp Pro Ile His Pro Tyr Thr Lys Phe Arg Val
 10565 10570 10575
 Pro Asp Leu Leu Glu Gly Cys Gln Tyr Glu Phe Arg Val Ser Ala Glu
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 Asn Glu Ile Gly Ile Gly Asp Pro Ser Pro Pro Ser Lys Pro Val Phe
 10595 10600 10605
 Ala Lys Asp Pro Ile Ala Lys Pro Ser Pro Pro Val Asn Pro Glu Ala
 10610 10615 10620 1
 Ile Asp Thr Thr Cys Asn Ser Val Asp Leu Thr Trp Gln Pro Pro Arg
 0625 10630 10635 10640

His	Asp	Gly	Gly	Ser	Lys	Ile	Leu	Gly	Tyr	Ile	Val	Glu	Tyr	Gln	Lys	
				10645					10650					10655		
Val	Gly	Asp	Glu	Glu	Trp	Arg	Arg	Ala	Asn	His	Thr	Pro	Glu	Ser	Cys	
				10660				10665						10670		
Pro	Glu	Thr	Lys	Tyr	Lys	Val	Thr	Gly	Leu	Arg	Asp	Gly	Gln	Thr	Tyr	
				10675			10680					10685				
Lys	Phe	Arg	Val	Leu	Ala	Val	Asn	Ala	Ala	Gly	Glu	Ser	Asp	Pro	Ala	
				10690		10695				10700						1
His	Val	Pro	Glu	Pro	Val	Leu	Val	Lys	Asp	Arg	Leu	Glu	Pro	Pro	Glu	
0705				10710				10715						10720		
Leu	Ile	Leu	Asp	Ala	Asn	Met	Ala	Arg	Glu	Gln	His	Ile	Lys	Val	Gly	
				10725				10730					10735			
Asp	Thr	Leu	Arg	Leu	Ser	Ala	Ile	Ile	Lys	Gly	Val	Pro	Phe	Pro	Lys	
				10740				10745				10750				
Val	Thr	Trp	Lys	Lys	Glu	Asp	Arg	Ala	Pro	Thr	Lys	Ala	Arg	Ile		
				10755			10760				10765					
Asp	Val	Thr	Pro	Val	Gly	Ser	Lys	Leu	Glu	Ile	Arg	Asn	Ala	Ala	His	
				10770		10775				10780						1
Glu	Asp	Gly	Gly	Ile	Tyr	Ser	Leu	Thr	Val	Glu	Asn	Pro	Ala	Gly	Ser	
0785				10790				10795						10800		
Lys	Thr	Val	Ser	Val	Lys	Val	Leu	Val	Leu	Asp	Lys	Pro	Gly	Pro	Pro	
				10805				10810					10815			
Arg	Asp	Leu	Glu	Val	Ser	Glu	Ile	Arg	Lys	Asp	Ser	Cys	Tyr	Leu	Thr	
				10820			10825					10830				
Trp	Lys	Glu	Pro	Leu	Asp	Asp	Gly	Gly	Ser	Val	Ile	Thr	Asn	Tyr	Val	
				10835			10840			10845						
Val	Glu	Arg	Arg	Asp	Val	Ala	Ser	Ala	Gln	Trp	Ser	Pro	Leu	Ser	Ala	
				10850		10855				10860						1
Thr	Ser	Lys	Lys	Lys	Ser	His	Phe	Ala	Lys	His	Leu	Asn	Glu	Gly	Asn	
0865				10870				10875						10880		
Gln	Tyr	Leu	Phe	Arg	Val	Ala	Ala	Glu	Asn	Gln	Tyr	Gly	Arg	Gly	Pro	
				10885				10890				10895				
Phe	Val	Glu	Thr	Pro	Lys	Pro	Ile	Lys	Ala	Leu	Asp	Pro	Leu	His	Pro	
				10900			10905				10910					
Pro	Gly	Pro	Pro	Lys	Asp	Leu	His	His	Val	Asp	Val	Asp	Lys	Thr	Glu	
				10915			10920				10925					
Val	Ser	Leu	Val	Trp	Asn	Lys	Pro	Asp	Arg	Asp	Gly	Gly	Ser	Pro	Ile	
				10930		10935				10940						1
Thr	Gly	Tyr	Leu	Val	Glu	Tyr	Gln	Glu	Glu	Gly	Thr	Gln	Asp	Trp	Ile	
0945				10950				10955						10960		
Lys	Phe	Lys	Thr	Val	Thr	Asn	Leu	Glu	Cys	Val	Val	Thr	Gly	Leu	Gln	

Ser Pro Val Ile Asn Tyr Ile Val Glu Lys Gln Asp Thr Arg Lys Asp
 11140 11145 11150
 Thr Trp Gly Val Val Ser Ser Gly Ser Ser Lys Thr Lys Leu Lys Ile
 11155 11160 11165
 Pro His Leu Gln Lys Gly Cys Glu Tyr Val Phe Arg Val Arg Ala Glu
 11170 11175 11180 1
 Asn Lys Ile Gly Val Gly Pro Pro Leu Asp Ser Thr Pro Thr Val Ala
 11185 11190 11195 11200
 Lys His Lys Phe Ser Pro Pro Ser Pro Pro Gly Lys Pro Val Val Thr
 11205 11210 11215
 Asp Ile Thr Glu Asn Ala Ala Thr Val Ser Trp Thr Leu Pro Lys Ser
 11220 11225 11230
 Asp Gly Gly Ser Pro Ile Thr Gly Tyr Tyr Met Glu Arg Arg Glu Val
 11235 11240 11245
 Thr Gly Lys Trp Val Arg Val Asn Lys Thr Pro Ile Ala Asp Leu Lys
 11250 11255 11260 1
 Phe Arg Val Thr Gly Leu Tyr Glu Gly Asn Thr Tyr Glu Phe Arg Val
 11265 11270 11275 11280
 Phe Ala Glu Asn Leu Ala Gly Leu Ser Lys Pro Ser Pro Ser Ser Asp
 11285 11290 11295
 Pro Ile Lys Ala Cys Arg Pro Ile Lys Pro Pro Gly Pro Pro Ile Asn
 11300 11305 11310
 Pro Lys Leu Lys Asp Lys Ser Arg Glu Thr Ala Asp Leu Val Trp Thr
 11315 11320 11325
 Lys Pro Leu Ser Asp Gly Gly Ser Pro Ile Leu Gly Tyr Val Val Glu
 11330 11335 11340 1
 Cys Gln Lys Pro Gly Thr Ala Gln Trp Asn Arg Ile Asn Lys Asp Glu
 11345 11350 11355 11360
 Leu Ile Arg Gln Cys Ala Phe Arg Val Pro Gly Leu Ile Glu Gly Asn
 11365 11370 11375
 Glu Tyr Arg Phe Arg Ile Lys Ala Ala Asn Ile Val Gly Glu Gly Glu
 11380 11385 11390
 Pro Arg Glu Leu Ala Glu Ser Val Ile Ala Lys Asp Ile Leu His Pro
 11395 11400 11405
 Pro Glu Val Glu Leu Asp Val Thr Cys Arg Asp Val Ile Thr Val Arg
 11410 11415 11420 1
 Val Gly Gln Thr Ile Arg Ile Leu Ala Arg Val Lys Gly Arg Pro Glu
 11425 11430 11435 11440
 Pro Asp Ile Thr Trp Thr Lys Glu Gly Lys Val Leu Val Arg Glu Lys
 11445 11450 11455
 Arg Val Asp Leu Ile Gln Asp Leu Pro Arg Val Glu Leu Gln Ile Lys
 11460 11465 11470
 Glu Ala Val Arg Ala Asp His Gly Lys Tyr Ile Ile Ser Ala Lys Asn
 11475 11480 11485
 Ser Ser Gly His Ala Gln Gly Ser Ala Ile Val Asn Val Leu Asp Arg
 11490 11495 11500 1
 Pro Gly Pro Cys Gln Asn Leu Lys Val Thr Asn Val Thr Lys Glu Asn
 1505 11510 11515 11520
 Cys Thr Ile Ser Trp Glu Asn Pro Leu Asp Asn Gly Gly Ser Glu Ile
 11525 11530 11535
 Thr Asn Phe Ile Val Glu Tyr Arg Lys Pro Asn Gln Lys Gly Trp Ser
 11540 11545 11550
 Ile Val Ala Ser Asp Val Thr Lys Arg Leu Ile Lys Ala Asn Leu Leu
 11555 11560 11565
 Ala Asn Asn Glu Tyr Tyr Phe Arg Val Cys Ala Glu Asn Lys Val Gly
 11570 11575 11580 1
 Val Gly Pro Thr Ile Glu Thr Lys Thr Pro Ile Leu Ala Ile Asn Pro
 1585 11590 11595 11600
 Ile Asp Arg Pro Gly Glu Pro Glu Asn Leu His Ile Ala Asp Lys Gly
 11605 11610 11615
 Lys Thr Phe Val Tyr Leu Lys Trp Arg Arg Pro Asp Tyr Asp Gly Gly
 11620 11625 11630

Ser Pro Asn Leu Ser Tyr His Val Glu Arg Arg Leu Lys Gly Ser Asp
 11635 11640 11645
 Asp Trp Glu Arg Val His Lys Gly Ser Ile Lys Glu Thr His Tyr Met
 11650 11655 11660 1
 Val Asp Arg Cys Val Glu Asn Gln Ile Tyr Glu Phe Arg Val Gln Thr
 1665 11670 11675 11680
 Lys Asn Glu Gly Gly Glu Ser Asp Trp Val Lys Thr Glu Glu Val Val
 11685 11690 11695
 Val Lys Glu Asp Leu Gln Lys Pro Val Leu Asp Leu Lys Leu Ser Gly
 11700 11705 11710
 Val Leu Thr Val Lys Ala Gly Asp Thr Ile Arg Leu Glu Ala Gly Val
 11715 11720 11725
 Arg Gly Lys Pro Phe Pro Glu Val Ala Trp Thr Lys Asp Lys Asp Ala
 11730 11735 11740 1
 Thr Asp Leu Thr Arg Ser Pro Arg Val Lys Ile Asp Thr Arg Ala Asp
 1745 11750 11755 11760
 Ser Ser Lys Phe Ser Leu Thr Lys Ala Lys Arg Ser Asp Gly Gly Lys
 11765 11770 11775
 Tyr Val Val Thr Ala Thr Asn Thr Ala Gly Ser Phe Val Ala Tyr Ala
 11780 11785 11790
 Thr Val Asn Val Leu Asp Lys Pro Gly Pro Val Arg Asn Leu Lys Ile
 11795 11800 11805
 Val Asp Val Ser Ser Asp Arg Cys Thr Val Cys Trp Asp Pro Pro Glu
 11810 11815 11820 1
 Asp Asp Gly Gly Cys Glu Ile Gln Asn Tyr Ile Leu Glu Lys Cys Glu
 1825 11830 11835 11840
 Thr Lys Arg Met Val Trp Ser Thr Tyr Ser Ala Thr Val Leu Thr Pro
 11845 11850 11855
 Gly Thr Thr Val Thr Arg Leu Ile Glu Gly Asn Glu Tyr Ile Phe Arg
 11860 11865 11870
 Val Arg Ala Glu Asn Lys Ile Gly Thr Gly Pro Pro Thr Glu Ser Lys
 11875 11880 11885
 Pro Val Ile Ala Lys Thr Lys Tyr Asp Lys Pro Gly Arg Pro Asp Pro
 11890 11895 11900 1
 Pro Glu Val Thr Lys Val Ser Lys Glu Glu Met Thr Val Val Trp Asn
 1905 11910 11915 11920
 Pro Pro Glu Tyr Asp Gly Gly Lys Ser Ile Thr Gly Tyr Phe Leu Glu
 11925 11930 11935
 Lys Lys Glu Lys His Ser Thr Arg Trp Val Pro Val Asn Lys Ser Ala
 11940 11945 11950
 Ile Pro Glu Arg Arg Met Lys Val Gln Asn Leu Leu Pro Asp His Glu
 11955 11960 11965
 Tyr Gln Phe Arg Val Lys Ala Glu Asn Glu Ile Gly Ile Gly Glu Pro
 11970 11975 11980 1
 Ser Leu Pro Ser Arg Pro Val Val Ala Lys Asp Pro Ile Glu Pro Pro
 1985 11990 11995 12000
 Gly Pro Pro Thr Asn Phe Arg Val Val Asp Thr Thr Lys His Ser Ile
 12005 12010 12015
 Thr Leu Gly Trp Gly Lys Pro Val Tyr Asp Gly Gly Ala Pro Ile Ile
 12020 12025 12030
 Gly Tyr Val Val Glu Met Arg Pro Lys Ile Ala Asp Ala Ser Pro Asp
 12035 12040 12045
 Glu Gly Trp Lys Arg Cys Asn Ala Ala Ala Gln Leu Val Arg Lys Glu
 12050 12055 12060 1
 Phe Thr Val Thr Ser Leu Asp Glu Asn Gln Glu Tyr Glu Phe Arg Val
 2065 12070 12075 12080
 Cys Ala Gln Asn Gln Val Gly Ile Gly Arg Pro Ala Glu Leu Lys Glu
 12085 12090 12095
 Ala Ile Lys Pro Lys Glu Ile Leu Glu Pro Pro Glu Ile Asp Leu Asp
 12100 12105 12110
 Ala Ser Met Arg Lys Leu Val Ile Val Arg Ala Gly Cys Pro Ile Arg
 12115 12120 12125

Leu Phe Ala Ile Val Arg Gly Arg Pro Ala Pro Lys Val Thr Trp Arg 1
 12130 12135 12140
 Lys Val Gly Ile Asp Asn Val Val Arg Lys Gly Gln Val Asp Leu Val 1
 2145 12150 12155 12160
 Asp Thr Met Ala Phe Leu Val Ile Pro Asn Ser Thr Arg Asp Asp Ser
 12165 12170 12175
 Gly Lys Tyr Ser Leu Thr Leu Val Asn Pro Ala Gly Glu Lys Ala Val
 12180 12185 12190
 Phe Val Asn Val Arg Val Leu Asp Thr Pro Gly Pro Val Ser Asp Leu
 12195 12200 12205
 Lys Val Ser Asp Val Thr Lys Thr Ser Cys His Val Ser Trp Ala Pro 1
 12210 12215 12220
 Pro Glu Asn Asp Gly Gly Ser Gln Val Thr His Tyr Ile Val Glu Lys 1
 2225 12230 12235 12240
 Arg Glu Ala Asp Arg Lys Thr Trp Ser Thr Val Thr Pro Glu Val Lys
 12245 12250 12255
 Lys Thr Ser Phe His Val Thr Asn Leu Val Pro Gly Asn Glu Tyr Tyr
 12260 12265 12270
 Phe Arg Val Thr Ala Val Asn Glu Tyr Gly Pro Gly Val Pro Thr Asp
 12275 12280 12285
 Val Pro Lys Pro Val Leu Ala Ser Asp Pro Leu Ser Glu Pro Asp Pro 1
 12290 12295 12300
 Pro Arg Lys Leu Glu Ala Thr Glu Met Thr Lys Asn Ser Ala Thr Leu 1
 2305 12310 12315 12320
 Ala Trp Leu Pro Pro Leu Arg Asp Gly Gly Ala Lys Ile Asp Gly Tyr
 12325 12330 12335
 Ile Ile Ser Tyr Arg Glu Glu Glu Gln Pro Ala Asp Arg Trp Thr Glu
 12340 12345 12350
 Tyr Ser Val Val Lys Asp Leu Ser Leu Val Val Thr Gly Leu Lys Glu
 12355 12360 12365
 Gly Lys Lys Tyr Lys Phe Arg Val Ala Ala Arg Asn Ala Val Gly Val 1
 12370 12375 12380
 Ser Leu Pro Arg Glu Ala Glu Gly Val Tyr Glu Ala Lys Glu Gln Leu 1
 2385 12390 12395 12400
 Leu Pro Pro Lys Ile Leu Met Pro Glu Gln Ile Thr Ile Lys Ala Gly
 12405 12410 12415
 Lys Lys Leu Arg Ile Glu Ala His Val Tyr Gly Lys Pro His Pro Thr
 12420 12425 12430
 Cys Lys Trp Lys Lys Gly Glu Asp Glu Val Val Thr Ser Ser His Leu
 12435 12440 12445
 Ala Val His Lys Ala Asp Ser Ser Ser Ile Leu Ile Ile Lys Asp Val 1
 12450 12455 12460
 Thr Arg Lys Asp Ser Gly Tyr Tyr Ser Leu Thr Ala Glu Asn Ser Ser 1
 2465 12470 12475 12480
 Gly Thr Asp Thr Gln Lys Ile Lys Val Val Val Met Asp Ala Pro Gly
 12485 12490 12495
 Pro Pro Gln Pro Pro Phe Asp Ile Ser Asp Ile Asp Ala Asp Ala Cys
 12500 12505 12510
 Ser Leu Ser Trp His Ile Pro Leu Glu Asp Gly Gly Ser Asn Ile Thr
 12515 12520 12525
 Asn Tyr Ile Val Glu Lys Cys Asp Val Ser Arg Gly Asp Trp Val Thr 1
 12530 12535 12540
 Ala Leu Ala Ser Val Thr Lys Thr Ser Cys Arg Val Gly Lys Leu Ile
 2545 12550 12555 12560
 Pro Gly Gln Glu Tyr Ile Phe Arg Val Arg Ala Glu Asn Arg Phe Gly
 12565 12570 12575
 Ile Ser Glu Pro Leu Thr Ser Pro Lys Met Val Ala Gln Phe Pro Phe
 12580 12585 12590
 Gly Val Pro Ser Glu Pro Lys Asn Ala Arg Val Thr Lys Val Asn Lys
 12595 12600 12605
 Asp Cys Ile Phe Val Ala Trp Asp Arg Pro Asp Ser Asp Gly Gly Ser 1
 12610 12615 12620

Pro Ile Ile Gly Tyr Leu Ile Glu Arg Lys Glu Arg Asn Ser Leu Leu
 2625 12630 12635 12640
 Trp Val Lys Ala Asn Asp Thr Leu Val Arg Ser Thr Glu Tyr Pro Cys
 12645 12650 12655
 Ala Gly Leu Val Glu Gly Leu Glu Tyr Ser Phe Arg Ile Tyr Ala Leu
 12660 12665 12670
 Asn Lys Ala Gly Ser Ser Pro Pro Ser Lys Pro Thr Glu Tyr Val Thr
 12675 12680 12685
 Ala Arg Met Pro Val Asp Pro Pro Gly Lys Pro Glu Val Ile Asp Val
 12690 12695 12700 1
 Thr Lys Ser Thr Val Ser Leu Ile Trp Ala Arg Pro Lys His Asp Gly
 2705 12710 12715 12720
 Gly Ser Lys Ile Ile Gly Tyr Phe Val Glu Ala Cys Lys Leu Pro Gly
 12725 12730 12735
 Asp Lys Trp Val Arg Cys Asn Thr Ala Pro His Gln Ile Pro Gln Glu
 12740 12745 12750
 Glu Tyr Thr Ala Thr Gly Leu Glu Glu Lys Ala Gln Tyr Gln Phe Arg
 12755 12760 12765
 Ala Ile Ala Arg Thr Ala Val Asn Ile Ser Pro Pro Ser Glu Pro Ser
 12770 12775 12780 1
 Asp Pro Val Thr Ile Leu Ala Glu Asn Val Pro Pro Arg Ile Asp Leu
 2785 12790 12795 12800
 Ser Val Ala Met Lys Ser Leu Leu Thr Val Lys Ala Gly Thr Asn Val
 12805 12810 12815
 Cys Leu Asp Ala Thr Val Phe Gly Lys Pro Met Pro Thr Val Ser Trp
 12820 12825 12830
 Lys Lys Asp Gly Thr Leu Leu Lys Pro Ala Glu Gly Ile Lys Met Ala
 12835 12840 12845
 Met Gln Arg Asn Leu Cys Thr Leu Glu Leu Phe Ser Val Asn Arg Lys
 12850 12855 12860 1
 Asp Ser Gly Asp Tyr Thr Ile Thr Ala Glu Asn Ser Ser Gly Ser Lys
 2865 12870 12875 12880
 Ser Ala Thr Ile Lys Leu Lys Val Leu Asp Lys Pro Gly Pro Pro Ala
 12885 12890 12895
 Ser Val Lys Ile Asn Lys Met Tyr Ser Asp Arg Ala Met Leu Ser Trp
 12900 12905 12910
 Glu Pro Pro Leu Glu Asp Gly Gly Ser Glu Ile Thr Asn Tyr Ile Val
 12915 12920 12925
 Asp Lys Arg Glu Thr Ser Arg Pro Asn Trp Ala Gln Val Ser Ala Thr
 12930 12935 12940 1
 Val Pro Ile Thr Ser Cys Ser Val Glu Lys Leu Ile Glu Gly His Glu
 2945 12950 12955 12960
 Tyr Gln Phe Arg Ile Cys Ala Glu Asn Lys Tyr Gly Val Gly Asp Pro
 12965 12970 12975
 Val Phe Thr Glu Pro Ala Ile Ala Lys Asn Pro Tyr Asp Pro Pro Gly
 12980 12985 12990
 Arg Cys Asp Pro Pro Val Ile Ser Asn Ile Thr Lys Asp His Met Thr
 12995 13000 13005
 Val Ser Trp Lys Pro Pro Ala Asp Asp Gly Gly Ser Pro Ile Thr Gly
 13010 13015 13020 1
 Tyr Leu Leu Glu Lys Arg Glu Thr Gln Ala Val Asn Trp Thr Lys Val
 3025 13030 13035 13040
 Asn Arg Lys Pro Ile Ile Glu Arg Thr Leu Lys Ala Thr Gly Leu Gln
 13045 13050 13055
 Glu Gly Thr Glu Tyr Glu Phe Arg Val Thr Ala Ile Asn Lys Ala Gly
 13060 13065 13070
 Pro Gly Lys Pro Ser Asp Ala Ser Lys Ala Ala Tyr Ala Arg Asp Pro
 13075 13080 13085
 Gln Tyr Pro Pro Ala Pro Pro Ala Phe Pro Lys Val Tyr Asp Thr Thr
 13090 13095 13100 1
 Arg Ser Ser Val Ser Leu Ser Trp Gly Lys Pro Ala Tyr Asp Gly Gly
 3105 13110 13115 13120

Ser Pro Ile Ile Gly Tyr Leu Val Glu Val Lys Arg Ala Asp Ser Asp
 13125 13130 13135
 Asn Trp Val Arg Cys Asn Leu Pro Gln Asn Leu Gln Lys Thr Arg Phe
 13140 13145 13150
 Glu Val Thr Gly Leu Met Glu Asp Thr Gln Tyr Gln Phe Arg Val Tyr
 13155 13160 13165
 Ala Val Asn Lys Ile Gly Tyr Ser Asp Pro Ser Asp Val Pro Asp Lys
 13170 13175 13180 1
 His Tyr Pro Lys Asp Ile Leu Ile Pro Pro Glu Gly Glu His Asp Ala
 3185 13190 13195 13200
 Asp Leu Arg Lys Thr Leu Ile Leu Arg Ala Gly Val Thr Met Arg Leu
 13205 13210 13215
 Tyr Val Pro Val Lys Gly Arg Pro Pro Pro Lys Ile Thr Trp Ser Lys
 13220 13225 13230
 Pro Asn Val Asn Leu Arg Asp Arg Ile Gly Leu Asp Ile Lys Ser Thr
 13235 13240 13245
 Asp Phe Asp Thr Phe Leu Arg Cys Glu Asn Val Asn Lys Tyr Asp Ala
 13250 13255 13260 1
 Gly Lys Tyr Ile Leu Thr Leu Glu Asn Ser Cys Gly Lys Lys Glu Tyr
 3265 13270 13275 13280
 Thr Ile Val Val Lys Val Leu Asp Thr Pro Gly Pro Pro Ile Asn Val
 13285 13290 13295
 Thr Val Lys Glu Ile Ser Lys Asp Ser Ala Tyr Val Thr Trp Glu Pro
 13300 13305 13310
 Pro Ile Ile Asp Gly Gly Ser Pro Ile Ile Asn Tyr Val Val Gln Lys
 13315 13320 13325
 Arg Asp Ala Glu Arg Lys Ser Trp Ser Thr Val Thr Thr Glu Cys Ser
 13330 13335 13340 1
 Lys Thr Ser Phe Arg Val Pro Asn Leu Glu Glu Gly Lys Ser Tyr Phe
 3345 13350 13355 13360
 Phe Arg Val Phe Ala Glu Asn Glu Tyr Gly Ile Gly Asp Pro Gly Glu
 13365 13370 13375
 Thr Arg Asp Ala Val Lys Ala Ser Gln Thr Pro Gly Pro Val Val Asp
 13380 13385 13390
 Leu Lys Val Arg Ser Val Ser Lys Ser Ser Cys Ser Ile Gly Trp Lys
 13395 13400 13405
 Lys Pro His Ser Asp Gly Gly Ser Arg Ile Ile Gly Tyr Val Val Asp
 13410 13415 13420 1
 Phe Leu Thr Glu Glu Asn Lys Trp Gln Arg Val Met Lys Ser Leu Ser
 3425 13430 13435 13440
 Leu Gln Tyr Ser Ala Lys Asp Leu Thr Glu Gly Lys Glu Tyr Thr Phe
 13445 13450 13455
 Arg Val Ser Ala Glu Asn Glu Asn Gly Glu Gly Thr Pro Ser Glu Ile
 13460 13465 13470
 Thr Val Val Ala Arg Asp Asp Val Val Ala Pro Asp Leu Asp Leu Lys
 13475 13480 13485
 Gly Leu Pro Asp Leu Cys Tyr Leu Ala Lys Glu Asn Ser Asn Phe Arg
 13490 13495 13500 1
 Leu Lys Ile Pro Ile Lys Gly Lys Pro Ala Pro Ser Val Ser Trp Lys
 3505 13510 13515 13520
 Lys Gly Glu Asp Pro Leu Ala Thr Asp Thr Arg Val Ser Val Glu Ser
 13525 13530 13535
 Ser Ala Val Asn Thr Thr Leu Ile Val Tyr Asp Cys Gln Lys Ser Asp
 13540 13545 13550
 Ala Gly Lys Tyr Thr Ile Thr Leu Lys Asn Val Ala Gly Thr Lys Glu
 13555 13560 13565
 Gly Thr Ile Ser Ile Lys Val Val Gly Lys Pro Gly Ile Pro Thr Gly
 13570 13575 13580 1
 Pro Ile Lys Phe Asp Glu Val Thr Ala Glu Ala Met Thr Leu Lys Trp
 3585 13590 13595 13600
 Ala Pro Pro Lys Asp Asp Gly Gly Ser Glu Ile Thr Asn Tyr Ile Leu
 13605 13610 13615

Glu Lys Arg Asp Ser Val Asn Asn Lys Trp Val Thr Cys Ala Ser Ala
 13620 13625 13630
 Val Gln Lys Thr Thr Phe Arg Val Thr Arg Leu His Glu Gly Met Glu
 13635 13640 13645
 Tyr Thr Phe Arg Val Ser Ala Glu Asn Lys Tyr Gly Val Gly Glu Gly
 13650 13655 13660 1
 Leu Lys Ser Glu Pro Ile Val Ala Arg His Pro Phe Asp Val Pro Asp
 3665 13670 13675 13680
 Ala Pro Pro Pro Asn Ile Val Asp Val Arg His Asp Ser Val Ser
 13685 13690 13695
 Leu Thr Trp Thr Asp Pro Lys Lys Thr Gly Gly Ser Pro Ile Thr Gly
 13700 13705 13710
 Tyr His Leu Glu Phe Lys Glu Arg Asn Ser Leu Leu Trp Lys Arg Ala
 13715 13720 13725
 Asn Lys Thr Pro Ile Arg Met Arg Asp Phe Lys Val Thr Gly Leu Thr
 13730 13735 13740 1
 Glu Gly Leu Glu Tyr Glu Phe Arg Val Met Ala Ile Asn Leu Ala Gly
 3745 13750 13755 13760
 Val Gly Lys Pro Ser Leu Pro Ser Glu Pro Val Val Ala Leu Asp Pro
 13765 13770 13775
 Ile Asp Pro Pro Gly Lys Pro Glu Val Ile Asn Ile Thr Arg Asn Ser
 13780 13785 13790
 Val Thr Leu Ile Trp Thr Glu Pro Lys Tyr Asp Gly Gly His Lys Leu
 13795 13800 13805
 Thr Gly Tyr Ile Val Glu Lys Arg Asp Leu Pro Ser Lys Ser Trp Met
 13810 13815 13820 1
 Lys Ala Asn His Val Asn Val Pro Glu Cys Ala Phe Thr Val Thr Asp
 3825 13830 13835 13840
 Leu Val Glu Gly Gly Lys Tyr Glu Phe Arg Ile Arg Ala Lys Asn Thr
 13845 13850 13855
 Ala Gly Ala Ile Ser Ala Pro Ser Glu Ser Thr Glu Thr Ile Ile Cys
 13860 13865 13870
 Lys Asp Glu Tyr Glu Ala Pro Thr Ile Val Leu Asp Pro Thr Ile Lys
 13875 13880 13885
 Asp Gly Leu Thr Ile Lys Ala Gly Asp Thr Ile Val Leu Asn Ala Ile
 13890 13895 13900 1
 Ser Ile Leu Gly Lys Pro Leu Pro Lys Ser Ser Trp Ser Lys Ala Gly
 3905 13910 13915 13920
 Lys Asp Ile Arg Pro Ser Asp Ile Thr Gln Ile Thr Ser Thr Pro Thr
 13925 13930 13935
 Ser Ser Met Leu Thr Ile Lys Tyr Ala Thr Arg Lys Asp Ala Gly Glu
 13940 13945 13950
 Tyr Thr Ile Thr Ala Thr Asn Pro Phe Gly Thr Lys Val Glu His Val
 13955 13960 13965
 Lys Val Thr Val Leu Asp Val Pro Gly Pro Pro Gly Pro Val Glu Ile
 13970 13975 13980 1
 Ser Asn Val Ser Ala Glu Lys Ala Thr Leu Thr Trp Thr Pro Pro Leu
 3985 13990 13995 14000
 Glu Asp Gly Gly Ser Pro Ile Lys Ser Tyr Ile Leu Glu Lys Arg Glu
 14005 14010 14015
 Thr Ser Arg Leu Leu Trp Thr Val Val Ser Glu Asp Ile Gln Ser Cys
 14020 14025 14030
 Arg His Val Ala Thr Lys Leu Ile Gln Gly Asn Glu Tyr Ile Phe Arg
 14035 14040 14045
 Val Ser Ala Val Asn His Tyr Gly Lys Gly Glu Pro Val Gln Ser Glu
 14050 14055 14060 1
 Pro Val Lys Met Val Asp Arg Phe Gly Pro Pro Gly Pro Pro Glu Lys
 4065 14070 14075 14080
 Pro Glu Val Ser Asn Val Thr Lys Asn Thr Ala Thr Val Ser Trp Lys
 14085 14090 14095
 Arg Pro Val Asp Asp Gly Gly Ser Glu Ile Thr Gly Tyr His Val Glu
 14100 14105 14110

Arg Arg Glu Lys Lys Ser Leu Arg Trp Val Arg Ala Ile Lys Thr Pro
 14115 14120 14125
 Val Ser Asp Leu Arg Cys Lys Val Thr Gly Leu Gln Glu Gly Ser Thr
 14130 14135 14140 1
 Tyr Glu Phe Arg Val Ser Ala Glu Asn Arg Ala Gly Ile Gly Pro Pro
 14145 14150 14155 14160
 Ser Glu Ala Ser Asp Ser Val Leu Met Lys Asp Ala Ala Tyr Pro Pro
 14165 14170 14175
 Gly Pro Pro Ser Asn Pro His Val Thr Asp Thr Thr Lys Lys Ser Ala
 14180 14185 14190
 Ser Leu Ala Trp Gly Lys Pro His Tyr Asp Gly Gly Leu Glu Ile Thr
 14195 14200 14205
 Gly Tyr Val Val Glu His Gln Lys Val Gly Asp Glu Ala Trp Ile Lys
 14210 14215 14220 1
 Asp Thr Thr Gly Thr Ala Leu Arg Ile Thr Gln Phe Val Val Pro Asp
 4225 14230 14235 14240
 Leu Gln Thr Lys Glu Lys Tyr Asn Phe Arg Ile Ser Ala Ile Asn Asp
 14245 14250 14255
 Ala Gly Val Gly Glu Pro Ala Val Ile Pro Asp Val Glu Ile Val Glu
 14260 14265 14270
 Arg Glu Met Ala Pro Asp Phe Glu Leu Asp Ala Glu Leu Arg Arg Thr
 14275 14280 14285
 Leu Val Val Arg Ala Gly Leu Ser Ile Arg Ile Phe Val Pro Ile Lys
 14290 14295 14300 1
 Gly Arg Pro Ala Pro Glu Val Thr Trp Thr Lys Asp Asn Ile Asn Leu
 4305 14310 14315 14320
 Lys Asn Arg Ala Asn Ile Glu Asn Thr Glu Ser Phe Thr Leu Leu Ile
 14325 14330 14335
 Ile Pro Glu Cys Asn Arg Tyr Asp Thr Gly Lys Phe Val Met Thr Ile
 14340 14345 14350
 Glu Asn Pro Ala Gly Lys Lys Ser Gly Phe Val Asn Val Arg Val Leu
 14355 14360 14365
 Asp Thr Pro Gly Pro Val Leu Asn Leu Arg Pro Thr Asp Ile Thr Lys
 14370 14375 14380 1
 Asp Ser Val Thr Leu His Trp Asp Leu Pro Leu Ile Asp Gly Gly Ser
 4385 14390 14395 14400
 Arg Ile Thr Asn Tyr Ile Val Glu Lys Arg Glu Ala Thr Arg Lys Ser
 14405 14410 14415
 Tyr Ser Thr Ala Thr Thr Lys Cys His Lys Cys Thr Tyr Lys Val Thr
 14420 14425 14430
 Gly Leu Ser Glu Gly Cys Glu Tyr Phe Phe Arg Val Met Ala Glu Asn
 14435 14440 14445
 Glu Tyr Gly Ile Gly Glu Pro Thr Glu Thr Thr Glu Pro Val Lys Ala
 14450 14455 14460 1
 Ser Glu Ala Pro Ser Pro Asp Ser Leu Asn Ile Met Asp Ile Thr
 4465 14470 14475 14480
 Lys Ser Thr Val Ser Leu Ala Trp Pro Lys Pro Lys His Asp Gly Gly
 14485 14490 14495
 Ser Lys Ile Thr Gly Tyr Val Ile Glu Ala Gln Arg Lys Gly Ser Asp
 14500 14505 14510
 Gln Trp Thr His Ile Thr Thr Val Lys Gly Leu Glu Cys Val Val Arg
 14515 14520 14525
 Asn Leu Thr Glu Gly Glu Glu Tyr Thr Phe Gln Val Met Ala Val Asn
 14530 14535 14540 1
 Ser Ala Gly Arg Ser Ala Pro Arg Glu Ser Arg Pro Val Ile Val Lys
 4545 14550 14555 14560
 Glu Gln Thr Met Leu Pro Glu Leu Asp Leu Arg Gly Ile Tyr Gln Lys
 14565 14570 14575
 Leu Val Ile Ala Lys Ala Gly Asp Asn Ile Lys Val Glu Ile Pro Val
 14580 14585 14590
 Leu Gly Arg Pro Lys Pro Thr Val Thr Trp Lys Lys Gly Asp Gln Ile
 14595 14600 14605

Leu Lys Gln Thr Gln Arg Val Asn Phe Glu Thr Thr Ala Thr Ser Thr 1
 14610 14615 14620
 Ile Leu Asn Ile Asn Glu Cys Val Arg Ser Asp Ser Gly Pro Tyr Pro
 14625 14630 14635 14640
 Leu Thr Ala Arg Asn Ile Val Gly Glu Val Gly Asp Val Ile Thr Ile
 14645 14650 14655
 Gln Val His Asp Ile Pro Gly Pro Thr Gly Pro Ile Lys Phe Asp
 14660 14665 14670
 Glu Val Ser Ser Asp Phe Val Thr Phe Ser Trp Asp Pro Pro Glu Asn
 14675 14680 14685
 Asp Gly Gly Val Pro Ile Ser Asn Tyr Val Val Glu Met Arg Gln Thr
 14690 14695 14700 1
 Asp Ser Thr Thr Trp Val Glu Leu Ala Thr Thr Val Ile Arg Thr Thr
 4705 14710 14715 14720
 Tyr Lys Ala Thr Arg Leu Thr Thr Gly Leu Glu Tyr Gln Phe Arg Val
 14725 14730 14735
 Lys Ala Gln Asn Arg Tyr Gly Val Gly Pro Gly Ile Thr Ser Ala Trp
 14740 14745 14750
 Ile Val Ala Asn Tyr Pro Phe Lys Val Pro Gly Pro Pro Gly Thr Pro
 14755 14760 14765
 Gln Val Thr Ala Val Thr Lys Asp Ser Met Thr Ile Ser Trp His Glu
 14770 14775 14780 1
 Pro Leu Ser Asp Gly Gly Ser Pro Ile Leu Gly Tyr His Val Glu Arg
 4785 14790 14795 14800
 Lys Glu Arg Asn Gly Ile Leu Trp Gln Thr Val Ser Lys Ala Leu Val
 14805 14810 14815
 Pro Gly Asn Ile Phe Lys Ser Ser Gly Leu Thr Asp Gly Ile Ala Tyr
 14820 14825 14830
 Glu Phe Arg Val Ile Ala Glu Asn Met Ala Gly Lys Ser Lys Pro Ser
 14835 14840 14845
 Lys Pro Ser Glu Pro Met Leu Ala Leu Asp Pro Ile Asp Pro Pro Gly
 14850 14855 14860 1
 Lys Pro Val Pro Leu Asn Ile Thr Arg His Thr Val Thr Leu Lys Trp
 4865 14870 14875 14880
 Ala Lys Pro Glu Tyr Thr Gly Gly Phe Lys Ile Thr Ser Tyr Ile Val
 14885 14890 14895
 Glu Lys Arg Asp Leu Pro Asn Gly Arg Trp Leu Lys Ala Asn Phe Ser
 14900 14905 14910
 Asn Ile Leu Glu Asn Glu Phe Thr Val Ser Gly Leu Thr Glu Asp Ala
 14915 14920 14925
 Ala Tyr Glu Phe Arg Val Ile Ala Lys Asn Ala Ala Gly Ala Ile Ser
 14930 14935 14940 1
 Pro Pro Ser Glu Pro Ser Asp Ala Ile Thr Cys Arg Asp Asp Val Glu
 4945 14950 14955 14960
 Ala Pro Lys Ile Lys Val Asp Val Lys Phe Lys Asp Thr Val Ile Leu
 14965 14970 14975
 Lys Ala Gly Glu Ala Phe Arg Leu Glu Ala Asp Val Ser Gly Arg Pro
 14980 14985 14990
 Pro Pro Thr Met Glu Trp Ser Lys Asp Gly Lys Glu Leu Glu Gly Thr
 14995 15000 15005
 Ala Lys Leu Glu Ile Lys Ile Ala Asp Phe Ser Thr Asn Leu Val Asn
 15010 15015 15020 1
 Lys Asp Ser Thr Arg Arg Asp Ser Gly Ala Tyr Thr Leu Thr Ala Thr
 5025 15030 15035 15040
 Asn Pro Gly Gly Phe Ala Lys His Ile Phe Asn Val Lys Val Leu Asp
 15045 15050 15055
 Arg Pro Gly Pro Pro Glu Gly Pro Leu Ala Val Thr Glu Val Thr Ser
 15060 15065 15070
 Glu Lys Cys Val Leu Ser Trp Phe Pro Pro Leu Asp Asp Gly Gly Ala
 15075 15080 15085
 Lys Ile Asp His Tyr Ile Val Gln Lys Arg Glu Thr Ser Arg Leu Ala
 15090 15095 15100 1

Trp Thr Asn Val Ala Ser Glu Val Gln Val Thr Lys Leu Lys Val Thr
 5105 15110 15115 15120
 Lys Leu Leu Lys Gly Asn Glu Tyr Ile Phe Arg Val Met Ala Val Asn
 15125 15130 15135
 Lys Tyr Gly Val Gly Glu Pro Leu Glu Ser Glu Pro Val Leu Ala Val
 15140 15145 15150
 Asn Pro Tyr Gly Pro Pro Asp Pro Pro Lys Asn Pro Glu Val Thr Thr
 15155 15160 15165
 Ile Thr Lys Asp Ser Met Val Val Cys Trp Gly His Pro Asp Ser Asp
 15170 15175 15180 1
 Gly Gly Ser Glu Ile Ile Asn Tyr Ile Val Glu Arg Asp Lys Ala
 5185 15190 15195 15200
 Gly Gln Arg Trp Ile Lys Cys Asn Lys Lys Thr Leu Thr Asp Leu Arg
 15205 15210 15215
 Tyr Lys Val Ser Gly Leu Thr Glu Gly His Glu Tyr Glu Phe Arg Ile
 15220 15225 15230
 Met Ala Glu Asn Ala Ala Gly Ile Ser Ala Pro Ser Pro Thr Ser Pro
 15235 15240 15245
 Phe Tyr Lys Ala Cys Asp Thr Val Phe Lys Pro Gly Pro Pro Gly Asn
 15250 15255 15260 1
 Pro Arg Val Leu Asp Thr Ser Arg Ser Ser Ile Ser Ile Ala Trp Asn
 5265 15270 15275 15280
 Lys Pro Ile Tyr Asp Gly Gly Ser Glu Ile Thr Gly Tyr Met Val Glu
 15285 15290 15295
 Ile Ala Leu Pro Glu Glu Asp Glu Trp Gln Ile Val Thr Pro Pro Ala
 15300 15305 15310
 Gly Leu Lys Ala Thr Ser Tyr Thr Ile Thr Gly Leu Thr Glu Asn Gln
 15315 15320 15325
 Glu Tyr Lys Ile Arg Ile Tyr Ala Met Asn Ser Glu Gly Leu Gly Glu
 15330 15335 15340 1
 Pro Ala Leu Val Pro Gly Thr Pro Lys Ala Glu Asp Arg Met Leu Pro
 5345 15350 15355 15360
 Pro Glu Ile Glu Leu Asp Ala Asp Leu Arg Lys Val Val Thr Ile Arg
 15365 15370 15375
 Ala Cys Cys Thr Leu Arg Leu Phe Val Pro Ile Lys Gly Arg Pro Asp
 15380 15385 15390
 Pro Glu Val Lys Trp Ala Arg Asp His Gly Glu Ser Leu Asp Lys Ala
 15395 15400 15405
 Ser Ile Glu Ser Ala Ser Ser Tyr Thr Leu Leu Ile Val Gly Asn Val
 15410 15415 15420 1
 Asn Arg Phe Asp Ser Gly Lys Tyr Ile Leu Thr Val Glu Asn Ser Ser
 5425 15430 15435 15440
 Gly Ser Lys Ser Ala Phe Val Asn Val Arg Val Leu Asp Thr Pro Gly
 15445 15450 15455
 Pro Pro Gln Asp Leu Lys Val Lys Glu Val Thr Lys Thr Ser Val Thr
 15460 15465 15470
 Leu Thr Trp Asp Pro Pro Leu Leu Asp Gly Gly Ser Lys Ile Lys Asn
 15475 15480 15485
 Tyr Ile Val Glu Lys Arg Glu Ser Thr Arg Lys Ala Tyr Ser Thr Val
 15490 15495 15500 1
 Ala Thr Asn Cys His Lys Thr Ser Trp Lys Val Asp Gln Leu Gln Glu
 5505 15510 15515 15520
 Gly Cys Ser Tyr Tyr Phe Arg Val Leu Ala Glu Asn Glu Tyr Gly Ile
 15525 15530 15535
 Gly Leu Pro Ala Glu Thr Ala Glu Ser Val Lys Ala Ser Glu Arg Pro
 15540 15545 15550
 Leu Pro Pro Gly Lys Ile Thr Leu Met Asp Val Thr Arg Asn Ser Val
 15555 15560 15565
 Ser Leu Ser Trp Glu Lys Pro Glu His Asp Gly Gly Ser Arg Ile Leu
 15570 15575 15580 1
 Gly Tyr Ile Val Glu Met Gln Thr Lys Gly Ser Asp Lys Trp Ala Thr
 5585 15590 15595 15600

Cys Ala Thr Val Lys Val Thr Glu Ala Thr Ile Thr Gly Leu Ile Gln
 15605 15610 15615
 Gly Glu Glu Tyr Ser Phe Arg Val Ser Ala Gln Asn Glu Lys Gly Ile
 15620 15625 15630
 Ser Asp Pro Arg Gln Leu Ser Val Pro Val Ile Ala Lys Asp Leu Val
 15635 15640 15645
 Ile Pro Pro Ala Phe Lys Leu Leu Phe Asn Thr Phe Thr Val Leu Ala
 15650 15655 15660 1
 Gly Glu Asp Leu Lys Val Asp Val Pro Phe Ile Gly Arg Pro Thr Pro
 5665 15670 15675 15680
 Ala Val Thr Trp His Lys Asp Asn Val Pro Leu Lys Gln Thr Thr Arg
 15685 15690 15695
 Val Asn Ala Glu Ser Thr Glu Asn Asn Ser Leu Leu Thr Ile Lys Asp
 15700 15705 15710
 Ala Cys Arg Glu Asp Val Gly His Tyr Val Val Lys Leu Thr Asn Ser
 15715 15720 15725
 Ala Gly Glu Ala Ile Glu Thr Leu Asn Val Ile Val Leu Asp Lys Pro
 15730 15735 15740 1
 Gly Pro Pro Thr Gly Pro Val Lys Met Asp Glu Val Thr Ala Asp Ser
 5745 15750 15755 15760
 Ile Thr Leu Ser Trp Gly Pro Pro Lys Tyr Asp Gly Gly Ser Ser Ile
 15765 15770 15775
 Asn Asn Tyr Ile Val Glu Lys Arg Asp Thr Ser Thr Thr Trp Gln
 15780 15785 15790
 Ile Val Ser Ala Thr Val Ala Arg Thr Thr Ile Lys Ala Cys Arg Leu
 15795 15800 15805
 Lys Thr Gly Cys Glu Tyr Gln Phe Arg Ile Ala Ala Glu Asn Arg Tyr
 15810 15815 15820 1
 Gly Lys Ser Thr Tyr Leu Asn Ser Glu Pro Thr Val Ala Gln Tyr Pro
 5825 15830 15835 15840
 Phe Lys Val Pro Gly Pro Pro Gly Thr Pro Val Val Thr Leu Ser Ser
 15845 15850 15855
 Arg Asp Ser Met Glu Val Gln Trp Asn Glu Pro Ile Ser Asp Gly Gly
 15860 15865 15870
 Ser Arg Val Ile Gly Tyr His Leu Glu Arg Lys Glu Arg Asn Ser Ile
 15875 15880 15885
 Leu Trp Val Lys Leu Asn Lys Thr Pro Ile Pro Gln Thr Lys Phe Lys
 15890 15895 15900 1
 Thr Thr Gly Leu Glu Glu Gly Val Glu Tyr Glu Phe Arg Val Ser Ala
 5905 15910 15915 15920
 Glu Asn Ile Val Gly Ile Gly Lys Pro Ser Lys Val Ser Glu Cys Tyr
 15925 15930 15935
 Val Ala Arg Asp Pro Cys Asp Pro Pro Gly Arg Pro Glu Ala Ile Ile
 15940 15945 15950
 Val Thr Arg Asn Ser Val Thr Leu Gln Trp Lys Lys Pro Thr Tyr Asp
 15955 15960 15965
 Gly Gly Ser Lys Ile Thr Gly Tyr Ile Val Glu Lys Lys Glu Leu Pro
 15970 15975 15980 1
 Glu Gly Arg Trp Met Lys Ala Ser Phe Thr Asn Ile Ile Asp Thr His
 5985 15990 16000
 Phe Glu Val Thr Gly Leu Val Glu Asp His Arg Tyr Glu Phe Arg Val
 16005 16010 16015
 Ile Ala Arg Asn Ala Ala Gly Val Phe Ser Glu Pro Ser Glu Ser Thr
 16020 16025 16030
 Gly Ala Ile Thr Ala Arg Asp Glu Val Asp Pro Pro Arg Ile Ser Met
 16035 16040 16045
 Asp Pro Lys Tyr Lys Asp Thr Ile Val Val His Ala Gly Glu Ser Phe
 16050 16055 16060 1
 Lys Val Asp Ala Asp Ile Tyr Gly Lys Pro Ile Pro Thr Ile Gln Trp
 6065 16070 16075 16080
 Ile Lys Gly Asp Gln Glu Leu Ser Asn Thr Ala Arg Leu Glu Ile Lys
 16085 16090 16095

Ser Thr Asp Phe Ala Thr Ser Leu Ser Val Lys Asp Ala Val Arg Val
 16100 16105 16110
 Asp Ser Gly Asn Tyr Ile Leu Lys Ala Lys Asn Val Ala Gly Glu Arg
 16115 16120 16125
 Ser Val Thr Val Asn Val Lys Val Leu Asp Arg Pro Gly Pro Pro Glu
 16130 16135 16140 1
 Gly Pro Val Val Ile Ser Gly Val Thr Ala Glu Lys Cys Thr Leu Ala
 6145 16150 16155 16160
 Trp Lys Pro Pro Leu Gln Asp Gly Gly Ser Asp Ile Ile Asn Tyr Ile
 16165 16170 16175
 Val Glu Arg Arg Glu Thr Ser Arg Leu Val Trp Thr Val Val Asp Ala
 16180 16185 16190
 Asn Val Gln Thr Leu Ser Cys Lys Val Thr Lys Leu Leu Glu Gly Asn
 16195 16200 16205
 Glu Tyr Thr Phe Arg Ile Met Ala Val Asn Lys Tyr Gly Val Gly Glu
 16210 16215 16220 1
 Pro Leu Glu Ser Glu Pro Val Val Ala Lys Asn Pro Phe Val Val Pro
 6225 16230 16235 16240
 Asp Ala Pro Lys Ala Pro Glu Val Thr Thr Val Thr Lys Asp Ser Met
 16245 16250 16255
 Ile Val Val Trp Glu Arg Pro Ala Ser Asp Gly Gly Ser Glu Ile Leu
 16260 16265 16270
 Gly Tyr Val Leu Glu Lys Arg Asp Lys Glu Gly Ile Arg Trp Thr Arg
 16275 16280 16285
 Cys His Lys Arg Leu Ile Gly Glu Leu Arg Leu Arg Val Thr Gly Leu
 16290 16295 16300 1
 Ile Glu Asn His Asp Tyr Glu Phe Arg Val Ser Ala Glu Asn Ala Ala
 6305 16310 16315 16320
 Gly Leu Ser Glu Pro Ser Pro Pro Ser Ala Tyr Gln Lys Ala Cys Asp
 16325 16330 16335
 Pro Ile Tyr Lys Pro Gly Pro Pro Asn Asn Pro Lys Val Ile Asp Ile
 16340 16345 16350
 Thr Arg Ser Ser Val Phe Leu Ser Trp Ser Lys Pro Ile Tyr Asp Gly
 16355 16360 16365
 Gly Cys Glu Ile Gln Gly Tyr Ile Val Glu Lys Cys Asp Val Asn Val
 16370 16375 16380 1
 Gly Glu Trp Thr Met Cys Thr Pro Pro Thr Gly Ile Asn Lys Thr Asn
 6385 16390 16395 16400
 Ile Glu Val Glu Lys Leu Leu Glu Lys His Glu Tyr Asn Phe Arg Ile
 16405 16410 16415
 Cys Ala Ile Asn Lys Ala Gly Val Gly Glu His Ala Asp Val Pro Gly
 16420 16425 16430
 Pro Ile Ile Val Glu Glu Lys Leu Glu Ala Pro Asp Ile Asp Leu Asp
 16435 16440 16445
 Leu Glu Leu Arg Lys Ile Ile Asn Ile Arg Ala Gly Gly Ser Leu Arg
 16450 16455 16460 1
 Leu Phe Val Pro Ile Lys Gly Arg Pro Thr Pro Glu Val Lys Trp Gly
 6465 16470 16475 16480
 Lys Val Asp Gly Glu Ile Arg Asp Ala Ala Ile Ile Asp Val Thr Ser
 16485 16490 16495
 Ser Phe Thr Ser Leu Val Leu Asp Asn Val Asn Arg Tyr Asp Ser Gly
 16500 16505 16510
 Lys Tyr Thr Leu Thr Leu Glu Asn Ser Ser Gly Thr Lys Ser Ala Phe
 16515 16520 16525
 Val Thr Val Arg Val Leu Asp Thr Pro Ser Pro Pro Val Asn Leu Lys
 16530 16535 16540 1
 Val Thr Glu Ile Thr Lys Asp Ser Val Ser Ile Thr Trp Glu Pro Pro
 6545 16550 16555 16560
 Leu Leu Asp Gly Gly Ser Lys Ile Lys Asn Tyr Ile Val Glu Lys Arg
 16565 16570 16575
 Glu Ala Thr Arg Lys Ser Tyr Ala Ala Val Val Thr Asn Cys His Lys
 16580 16585 16590

Asn Ser Trp Lys Ile Asp Gln Leu Gln Glu Gly Cys Ser Tyr Tyr Phe
 16595 16600 16605
 Arg Val Thr Ala Glu Asn Glu Tyr Gly Ile Gly Leu Pro Ala Gln Thr
 16610 16615 16620 1
 Ala Asp Pro Ile Lys Val Ala Glu Val Pro Gln Pro Pro Gly Lys Ile
 6625 16630 16635 16640
 Thr Val Asp Asp Val Thr Arg Asn Ser Val Ser Leu Ser Trp Thr Lys
 16645 16650 16655
 Pro Glu His Asp Gly Gly Ser Lys Ile Ile Gln Tyr Ile Val Glu Met
 16660 16665 16670
 Gln Ala Lys His Ser Glu Lys Trp Ser Glu Cys Ala Arg Val Lys Ser
 16675 16680 16685
 Leu Gln Ala Val Ile Thr Asn Leu Thr Gln Gly Glu Tyr Leu Phe
 16690 16695 16700 1
 Arg Val Val Ala Val Asn Glu Lys Gly Arg Ser Asp Pro Arg Ser Leu
 6705 16710 16715 16720
 Ala Val Pro Ile Val Ala Lys Asp Leu Val Ile Glu Pro Asp Val Lys
 16725 16730 16735
 Pro Ala Phe Ser Ser Tyr Ser Val Gln Val Gly Gln Asp Leu Lys Ile
 16740 16745 16750
 Glu Val Pro Ile Ser Gly Arg Pro Lys Pro Thr Ile Thr Trp Thr Lys
 16755 16760 16765
 Asp Gly Leu Pro Leu Lys Gln Thr Thr Arg Ile Asn Val Thr Asp Ser
 16770 16775 16780 1
 Leu Asp Leu Thr Thr Leu Ser Ile Lys Glu Thr His Lys Asp Asp Gly
 6785 16790 16795 16800
 Gly Gln Tyr Gly Ile Thr Val Ala Asn Val Val Gly Gln Lys Thr Ala
 16805 16810 16815
 Ser Ile Glu Ile Val Thr Leu Asp Lys Pro Asp Pro Pro Lys Gly Pro
 16820 16825 16830
 Val Lys Phe Asp Asp Val Ser Ala Glu Ser Ile Thr Leu Ser Trp Asn
 16835 16840 16845
 Pro Pro Leu Tyr Thr Gly Gly Cys Gln Ile Thr Asn Tyr Ile Val Gln
 16850 16855 16860 1
 Lys Arg Asp Thr Thr Thr Val Trp Asp Val Val Ser Ala Thr Val
 6865 16870 16875 16880
 Ala Arg Thr Thr Leu Lys Val Thr Lys Leu Lys Thr Gly Thr Glu Tyr
 16885 16890 16895
 Gln Phe Arg Ile Phe Ala Glu Asn Arg Tyr Gly Gln Ser Phe Ala Leu
 16900 16905 16910
 Glu Ser Asp Pro Ile Val Ala Gln Tyr Pro Tyr Lys Glu Pro Gly Pro
 16915 16920 16925
 Pro Gly Thr Pro Phe Ala Thr Ala Ile Ser Lys Asp Ser Met Val Ile
 16930 16935 16940 1
 Gln Trp His Glu Pro Val Asn Asn Gly Gly Ser Pro Val Ile Gly Tyr
 6945 16950 16955 16960
 His Leu Glu Arg Lys Glu Arg Asn Ser Ile Leu Trp Thr Lys Val Asn
 16965 16970 16975
 Lys Thr Ile Ile His Asp Thr Gln Phe Lys Ala Gln Asn Leu Glu Glu
 16980 16985 16990
 Gly Ile Glu Tyr Glu Phe Arg Val Tyr Ala Glu Asn Ile Val Gly Val
 16995 17000 17005
 Gly Lys Ala Ser Lys Asn Ser Glu Cys Tyr Val Ala Arg Asp Pro Cys
 17010 17015 17020 1
 Asp Pro Pro Gly Thr Pro Glu Pro Ile Met Val Lys Arg Asn Glu Ile
 7025 17030 17035 17040
 Thr Leu Gln Trp Thr Lys Pro Val Tyr Asp Gly Gly Ser Met Ile Thr
 17045 17050 17055
 Gly Tyr Ile Val Glu Lys Arg Asp Leu Pro Asp Gly Arg Trp Met Lys
 17060 17065 17070
 Ala Ser Phe Thr Asn Val Ile Glu Thr Gln Phe Thr Val Ser Gly Leu
 17075 17080 17085

Thr Glu Asp Gln Arg Tyr Glu Phe Arg Val Ile Ala Lys Asn Ala Ala 1
 17090 17095 17100
 Gly Ala Ile Ser Lys Pro Ser Asp Ser Thr Gly Pro Ile Thr Ala Lys
 7105 17110 17115 17120
 Asp Glu Val Glu Leu Pro Arg Ile Ser Met Asp Pro Lys Phe Arg Asp
 17125 17130 17135
 Thr Ile Val Val Asn Ala Gly Glu Thr Phe Arg Leu Glu Ala Asp Val
 17140 17145 17150
 His Gly Lys Pro Leu Pro Thr Ile Glu Trp Leu Arg Gly Asp Lys Glu
 17155 17160 17165
 Ile Glu Glu Ser Ala Arg Cys Glu Ile Lys Asn Thr Asp Phe Lys Ala
 17170 17175 17180 1
 Leu Leu Ile Val Lys Asp Ala Ile Arg Ile Asp Gly Gly Gln Tyr Ile
 7185 17190 17195 17200
 Leu Arg Ala Ser Asn Val Ala Gly Ser Lys Ser Phe Pro Val Asn Val
 17205 17210 17215
 Lys Val Leu Asp Arg Pro Gly Pro Pro Glu Gly Pro Val Gln Val Thr
 17220 17225 17230
 Gly Val Thr Ser Glu Lys Cys Ser Leu Thr Trp Ser Pro Pro Leu Gln
 17235 17240 17245
 Asp Gly Gly Ser Asp Ile Ser His Tyr Val Val Glu Lys Arg Glu Thr
 17250 17255 17260 1
 Ser Arg Leu Ala Trp Thr Val Val Ala Ser Glu Val Val Thr Asn Ser
 7265 17270 17275 17280
 Leu Lys Val Thr Lys Leu Leu Glu Gly Asn Glu Tyr Val Phe Arg Ile
 17285 17290 17295
 Met Ala Val Asn Lys Tyr Gly Val Gly Glu Pro Leu Glu Ser Ala Pro
 17300 17305 17310
 Val Leu Met Lys Asn Pro Phe Val Leu Pro Gly Pro Pro Lys Ser Leu
 17315 17320 17325
 Glu Val Thr Asn Ile Ala Lys Asp Ser Met Thr Val Cys Trp Asn Arg
 17330 17335 17340 1
 Pro Asp Ser Asp Gly Gly Ser Glu Ile Ile Gly Tyr Ile Val Glu Lys
 7345 17350 17355 17360
 Arg Asp Arg Ser Gly Ile Arg Trp Ile Lys Cys Asn Lys Arg Arg Ile
 17365 17370 17375
 Thr Asp Leu Arg Leu Arg Val Thr Gly Leu Thr Glu Asp His Glu Tyr
 17380 17385 17390
 Glu Phe Arg Val Ser Ala Glu Asn Ala Ala Gly Val Gly Glu Pro Ser
 17395 17400 17405
 Pro Ala Thr Val Tyr Tyr Lys Ala Cys Asp Pro Val Phe Lys Pro Gly
 17410 17415 17420 1
 Pro Pro Thr Asn Ala His Ile Val Asp Thr Thr Lys Asn Ser Ile Thr
 7425 17430 17435 17440
 Leu Ala Trp Gly Lys Pro Ile Tyr Asp Gly Gly Ser Glu Ile Leu Gly
 17445 17450 17455
 Tyr Val Val Glu Ile Cys Lys Ala Asp Glu Glu Glu Trp Gln Ile Val
 17460 17465 17470
 Thr Pro Gln Thr Gly Leu Arg Val Thr Arg Phe Glu Ile Ser Lys Leu
 17475 17480 17485
 Thr Glu His Gln Glu Tyr Lys Ile Arg Val Cys Ala Leu Asn Lys Val
 17490 17495 17500 1
 Gly Leu Gly Glu Ala Thr Ser Val Pro Gly Thr Val Lys Pro Glu Asp
 7505 17510 17515 17520
 Lys Leu Glu Ala Pro Glu Leu Asp Leu Asp Ser Glu Leu Arg Lys Gly
 17525 17530 17535
 Ile Val Val Arg Ala Gly Gly Ser Ala Arg Ile His Ile Pro Phe Lys
 17540 17545 17550
 Gly Arg Pro Met Pro Glu Ile Thr Trp Ser Arg Glu Glu Gly Glu Phe
 17555 17560 17565
 Thr Asp Lys Val Gln Ile Glu Lys Gly Val Asn Tyr Thr Gln Leu Ser
 17570 17575 17580 1

Ile Asp Asn Cys Asp Arg Asn Asp Ala Gly Lys Tyr Ile Leu Lys Leu
 7585 17590 17595 17600
 Glu Asn Ser Ser Gly Ser Lys Ser Ala Phe Val Thr Val Lys Val Leu
 17605 17610 17615
 Asp Thr Pro Gly Pro Pro Gln Asn Leu Ala Val Lys Glu Val Arg Lys
 17620 17625 17630
 Asp Ser Ala Phe Leu Val Trp Glu Pro Pro Ile Ile Asp Gly Gly Ala
 17635 17640 17645
 Lys Val Lys Asn Tyr Val Ile Asp Lys Arg Glu Ser Thr Arg Lys Ala
 17650 17655 17660 1
 Tyr Ala Asn Val Ser Ser Lys Cys Ser Lys Thr Ser Phe Lys Val Glu
 7665 17670 17675 17680
 Asn Leu Thr Glu Gly Ala Ile Tyr Tyr Phe Arg Val Met Ala Glu Asn
 17685 17690 17695
 Glu Phe Gly Val Gly Val Pro Val Glu Thr Val Asp Ala Val Lys Ala
 17700 17705 17710
 Ala Glu Pro Pro Ser Pro Pro Gly Lys Val Thr Leu Thr Asp Val Ser
 17715 17720 17725
 Gln Thr Ser Ala Ser Leu Met Trp Glu Lys Pro Glu His Asp Gly Gly
 17730 17735 17740 1
 Ser Arg Val Leu Gly Tyr Val Val Glu Met Gln Pro Lys Gly Thr Glu
 7745 17750 17755 17760
 Lys Trp Ser Ile Val Ala Glu Ser Lys Val Cys Asn Ala Val Val Thr
 17765 17770 17775
 Gly Leu Ser Ser Gly Gln Glu Tyr Gln Phe Arg Val Lys Ala Tyr Asn
 17780 17785 17790
 Glu Lys Gly Lys Ser Asp Pro Arg Val Leu Gly Val Pro Val Ile Ala
 17795 17800 17805
 Lys Asp Leu Thr Ile Gln Pro Ser Leu Lys Leu Pro Phe Asn Thr Tyr
 17810 17815 17820 1
 Ser Ile Gln Ala Gly Glu Asp Leu Lys Ile Glu Ile Pro Val Ile Gly
 7825 17830 17835 17840
 Arg Pro Arg Pro Asn Ile Ser Trp Val Lys Asp Gly Glu Pro Leu Lys
 17845 17850 17855
 Gln Thr Thr Arg Val Asn Val Glu Glu Thr Ala Thr Ser Thr Val Leu
 17860 17865 17870
 His Ile Lys Glu Gly Asn Lys Asp Asp Phe Gly Lys Tyr Thr Val Thr
 17875 17880 17885
 Ala Thr Asn Ser Ala Gly Thr Ala Thr Glu Asn Leu Ser Val Ile Val
 17890 17895 17900 1
 Leu Glu Lys Pro Gly Pro Pro Val Gly Pro Val Arg Phe Asp Glu Val
 7905 17910 17915 17920
 Ser Ala Asp Phe Val Val Ile Ser Trp Glu Pro Pro Ala Tyr Thr Gly
 17925 17930 17935
 Gly Cys Gln Ile Ser Asn Tyr Ile Val Glu Lys Arg Asp Thr Thr Thr
 17940 17945 17950
 Thr Thr Trp His Met Val Ser Ala Thr Val Ala Arg Thr Thr Ile Lys
 17955 17960 17965
 Ile Thr Lys Leu Lys Thr Gly Thr Glu Tyr Gln Phe Arg Ile Phe Ala
 17970 17975 17980 1
 Glu Asn Arg Tyr Gly Lys Ser Ala Pro Leu Asp Ser Lys Ala Val Ile
 7985 17990 17995 18000
 Val Gln Tyr Pro Phe Lys Glu Pro Gly Pro Pro Gly Thr Pro Phe Val
 18005 18010 18015
 Thr Ser Ile Ser Lys Asp Gln Met Leu Val Gln Trp His Glu Pro Val
 18020 18025 18030
 Asn Asp Gly Gly Thr Lys Ile Ile Gly Tyr His Leu Glu Gln Lys Glu
 18035 18040 18045
 Lys Asn Ser Ile Leu Trp Val Lys Leu Asn Lys Thr Pro Ile Gln Asp
 18050 18055 18060 1
 Thr Lys Phe Lys Thr Thr Gly Leu Asp Glu Gly Leu Glu Tyr Glu Phe
 8065 18070 18075 18080

Lys Val Ser Ala Glu Asn Ile Val Gly Ile Gly Lys Pro Ser Lys Val
 18085 18090 18095
 Ser Glu Cys Phe Val Ala Arg Asp Pro Cys Asp Pro Pro Gly Arg Pro
 18100 18105 18110
 Glu Ala Ile Val Ile Thr Arg Asn Asn Val Thr Leu Lys Trp Lys Lys
 18115 18120 18125
 Pro Ala Tyr Asp Gly Gly Ser Lys Ile Thr Gly Tyr Ile Val Glu Lys
 18130 18135 18140
 Lys Asp Leu Pro Asp Gly Arg Trp Met Lys Ala Ser Phe Thr Asn Val
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 Leu Glu Thr Glu Phe Thr Val Ser Gly Leu Val Glu Asp Gln Arg Tyr
 18165 18170 18175
 Glu Phe Arg Val Ile Ala Arg Asn Ala Ala Gly Asn Phe Ser Glu Pro
 18180 18185 18190
 Ser Asp Ser Ser Gly Ala Ile Thr Ala Arg Asp Glu Ile Asp Ala Pro
 18195 18200 18205
 Asn Ala Ser Leu Asp Pro Lys Tyr Lys Asp Val Ile Val Val His Ala
 18210 18215 18220
 Gly Glu Thr Phe Val Leu Glu Ala Asp Ile Arg Gly Lys Pro Ile Pro
 8225 18230 18235 18240
 Asp Val Val Trp Ser Lys Asp Gly Lys Glu Leu Glu Glu Thr Ala Ala
 18245 18250 18255
 Arg Met Glu Ile Lys Ser Thr Ile Gln Lys Thr Thr Leu Val Val Lys
 18260 18265 18270
 Asp Cys Ile Arg Thr Asp Gly Gly Gln Tyr Ile Leu Lys Leu Ser Asn
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 Val Gly Gly Thr Lys Ser Ile Pro Ile Thr Val Lys Val Leu Asp Arg
 18290 18295 18300
 Pro Gly Ser Pro Glu Gly Pro Leu Lys Val Thr Gly Val Thr Ala Glu
 8305 18310 18315 18320
 Lys Cys Tyr Leu Ala Trp Asn Pro Pro Leu Gln Asp Gly Gly Ala Asn
 18325 18330 18335
 Ile Ser His Tyr Ile Ile Glu Lys Arg Glu Thr Ser Arg Leu Ser Trp
 18340 18345 18350
 Thr Gln Val Ser Thr Glu Val Gln Ala Leu Asn Tyr Lys Val Thr Lys
 18355 18360 18365
 Leu Leu Pro Gly Asn Glu Tyr Ile Phe Arg Val Met Ala Val Asn Lys
 18370 18375 18380
 Tyr Gly Ile Gly Glu Pro Leu Glu Ser Gly Pro Val Thr Ala Cys Asn
 8385 18390 18395 18400
 Pro Tyr Lys Pro Pro Gly Pro Pro Ser Thr Pro Glu Val Ser Ala Ile
 18405 18410 18415
 Thr Lys Asp Ser Met Val Val Thr Trp Ala Arg Pro Val Asp Asp Gly
 18420 18425 18430
 Gly Thr Glu Ile Glu Gly Tyr Ile Leu Glu Lys Arg Asp Lys Glu Gly
 18435 18440 18445
 Val Arg Trp Thr Lys Cys Asn Lys Lys Thr Leu Thr Asp Leu Arg Leu
 18450 18455 18460
 Arg Val Thr Gly Leu Thr Glu Gly His Ser Tyr Glu Phe Arg Val Ala
 8465 18470 18475 18480
 Ala Glu Asn Ala Ala Gly Val Gly Glu Pro Ser Glu Pro Ser Val Phe
 18485 18490 18495
 Tyr Arg Ala Cys Asp Ala Leu Tyr Pro Pro Gly Pro Pro Ser Asn Pro
 18500 18505 18510
 Lys Val Thr Asp Thr Ser Arg Ser Ser Val Ser Leu Ala Trp Ser Lys
 18515 18520 18525
 Pro Ile Tyr Asp Gly Gly Ala Pro Val Lys Gly Tyr Val Val Glu Val
 18530 18535 18540
 Lys Glu Ala Ala Ala Asp Glu Trp Thr Thr Cys Thr Pro Pro Thr Gly
 8545 18550 18555 18560
 Leu Gln Gly Lys Gln Phe Thr Val Thr Lys Leu Lys Glu Asn Thr Glu
 18565 18570 18575

Tyr Asn Phe Arg Ile Cys Ala Ile Asn Ser Glu Gly Val Gly Glu Pro
 18580 18585 18590
 Ala Thr Leu Pro Gly Ser Val Val Ala Gln Glu Arg Ile Glu Pro Pro
 18595 18600 18605
 Glu Ile Glu Leu Asp Ala Asp Leu Arg Lys Val Val Val Leu Arg Ala
 18610 18615 18620 1
 Ser Ala Thr Leu Arg Leu Phe Val Thr Ile Lys Gly Arg Pro Glu Pro
 8625 18630 18635 18640
 Glu Val Lys Trp Glu Lys Ala Glu Gly Ile Leu Thr Asp Arg Ala Gln
 18645 18650 18655
 Ile Glu Val Thr Ser Ser Phe Thr Met Leu Val Ile Asp Asn Val Thr
 18660 18665 18670
 Arg Phe Asp Ser Gly Arg Tyr Asn Leu Thr Leu Glu Asn Asn Ser Gly
 18675 18680 18685
 Ser Lys Thr Ala Phe Val Asn Val Arg Val Leu Asp Ser Pro Ser Ala
 18690 18695 18700 1
 Pro Val Asn Leu Thr Ile Arg Glu Val Lys Lys Asp Ser Val Thr Leu
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 Ser Trp Glu Pro Pro Leu Ile Asp Gly Gly Ala Lys Ile Thr Asn Tyr
 18725 18730 18735
 Ile Val Glu Lys Arg Glu Thr Thr Arg Lys Ala Tyr Ala Thr Ile Thr
 18740 18745 18750
 Asn Asn Cys Thr Lys Thr Thr Phe Arg Ile Glu Asn Leu Gln Glu Gly
 18755 18760 18765
 Cys Ser Tyr Tyr Phe Arg Val Leu Ala Ser Asn Glu Tyr Gly Ile Gly
 18770 18775 18780 1
 Leu Pro Ala Glu Thr Thr Glu Pro Val Lys Val Ser Glu Pro Pro Leu
 8785 18790 18795 18800
 Pro Pro Gly Arg Val Thr Leu Val Asp Val Thr Arg Asn Thr Ala Thr
 18805 18810 18815
 Ile Lys Trp Glu Lys Pro Glu Ser Asp Gly Gly Ser Lys Ile Thr Gly
 18820 18825 18830
 Tyr Val Val Glu Met Gln Thr Lys Gly Ser Glu Lys Trp Ser Thr Cys
 18835 18840 18845
 Thr Gln Val Lys Thr Leu Glu Ala Thr Ile Ser Gly Leu Thr Ala Gly
 18850 18855 18860 1
 Glu Glu Tyr Val Phe Arg Val Ala Ala Val Asn Glu Lys Gly Arg Ser
 8865 18870 18875 18880
 Asp Pro Arg Gln Leu Gly Val Pro Val Ile Ala Arg Asp Ile Glu Ile
 18885 18890 18895
 Lys Pro Ser Val Glu Leu Pro Phe His Thr Phe Asn Val Lys Ala Arg
 18900 18905 18910
 Glu Gln Leu Lys Ile Asp Val Pro Phe Lys Gly Arg Pro Gln Ala Thr
 18915 18920 18925
 Val Asn Trp Arg Lys Asp Gly Gln Thr Leu Lys Glu Thr Thr Arg Val
 18930 18935 18940 1
 Asn Val Ser Ser Ser Lys Thr Val Thr Ser Leu Ser Ile Lys Glu Ala
 8945 18950 18955 18960
 Ser Lys Glu Asp Val Gly Thr Tyr Glu Leu Cys Val Ser Asn Ser Ala
 18965 18970 18975
 Gly Ser Ile Thr Val Pro Ile Thr Ile Ile Val Leu Asp Arg Pro Gly
 18980 18985 18990
 Pro Pro Gly Pro Ile Arg Ile Asp Glu Val Ser Cys Asp Ser Ile Thr
 18995 19000 19005
 Ile Ser Trp Asn Pro Pro Glu Tyr Asp Gly Gly Cys Gln Ile Ser Asn
 19010 19015 19020 1
 Tyr Ile Val Glu Lys Lys Glu Thr Thr Ser Thr Thr Trp His Ile Val
 9025 19030 19035 19040
 Ser Gln Ala Val Ala Arg Thr Ser Ile Lys Ile Val Arg Leu Thr Thr
 19045 19050 19055
 Gly Ser Glu Tyr Gln Phe Arg Val Cys Ala Glu Asn Arg Tyr Gly Lys
 19060 19065 19070

Ser Ser Tyr Ser Glu Ser Ser Ala Val Val Ala Glu Tyr Pro Phe Ser
 19075 19080 19085
 Pro Pro Gly Pro Pro Gly Thr Pro Lys Val Val His Ala Thr Lys Ser
 19090 19095 19100
 Thr Met Leu Val Thr Trp Gln Val Pro Val Asn Asp Gly Gly Ser Arg
 9105 19110 19115 19120
 Val Ile Gly Tyr His Leu Glu Tyr Lys Glu Arg Ser Ser Ile Leu Trp
 19125 19130 19135
 Ser Lys Ala Asn Lys Ile Leu Ile Ala Asp Thr Gln Val Lys Val Ser
 19140 19145 19150
 Gly Leu Asp Glu Gly Leu Met Tyr Glu Tyr Arg Val Tyr Ala Glu Asn
 19155 19160 19165
 Ile Ala Gly Ile Gly Lys Cys Ser Lys Ser Cys Glu Pro Val Pro Ala
 19170 19175 19180
 Arg Asp Pro Cys Asp Pro Pro Gly Gln Pro Glu Val Thr Asn Ile Thr
 9185 19190 19195 19200
 Arg Lys Ser Val Ser Leu Lys Trp Ser Lys Pro His Tyr Asp Gly Gly
 19205 19210 19215
 Ala Lys Ile Thr Gly Tyr Ile Val Glu Arg Arg Glu Leu Pro Asp Gly
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 Arg Trp Leu Lys Cys Asn Tyr Thr Asn Ile Gln Glu Thr Tyr Phe Glu
 19235 19240 19245
 Val Thr Glu Leu Thr Glu Asp Gln Arg Tyr Glu Phe Arg Val Phe Ala
 19250 19255 19260
 Arg Asn Ala Ala Asp Ser Val Ser Glu Pro Ser Glu Ser Thr Gly Pro
 9265 19270 19275 19280
 Ile Ile Val Lys Asp Asp Val Glu Pro Pro Arg Val Met Met Asp Val
 19285 19290 19295
 Lys Phe Arg Asp Val Ile Val Val Lys Ala Gly Glu Val Leu Lys Ile
 19300 19305 19310
 Asn Ala Asp Ile Ala Gly Arg Pro Leu Pro Val Ile Ser Trp Ala Lys
 19315 19320 19325
 Asp Gly Ile Glu Ile Glu Glu Arg Ala Arg Thr Glu Ile Ile Ser Thr
 19330 19335 19340
 Asp Asn His Thr Leu Leu Thr Val Lys Asp Cys Ile Arg Arg Asp Thr
 9345 19350 19355 19360
 Gly Gln Tyr Val Leu Thr Leu Lys Asn Val Ala Gly Thr Arg Ser Val
 19365 19370 19375
 Ala Val Asn Cys Lys Val Leu Asp Lys Pro Gly Pro Pro Ala Gly Pro
 19380 19385 19390
 Leu Glu Ile Asn Gly Leu Thr Ala Glu Lys Cys Ser Leu Ser Trp Gly
 19395 19400 19405
 Arg Pro Gln Glu Asp Gly Gly Ala Asp Ile Asp Tyr Tyr His Arg Lys
 19410 19415 19420
 Lys Arg Glu Thr Ser His Leu Ala Trp Thr Ile Cys Glu Gly Glu Leu
 9425 19430 19435 19440
 Gln Met Thr Ser Cys Lys Val Thr Lys Leu Leu Lys Gly Asn Glu Tyr
 19445 19450 19455
 Ile Phe Arg Val Thr Gly Val Asn Lys Tyr Gly Val Gly Glu Pro Leu
 19460 19465 19470
 Glu Ser Val Ala Ile Lys Ala Leu Asp Pro Phe Thr Val Pro Ser Pro
 19475 19480 19485
 Pro Thr Ser Leu Glu Ile Thr Ser Val Thr Lys Glu Ser Met Thr Leu
 19490 19495 19500
 Cys Trp Ser Arg Pro Glu Ser Asp Gly Gly Ser Glu Ile Ser Gly Tyr
 9505 19510 19515 19520
 Ile Ile Glu Arg Arg Glu Lys Asn Ser Leu Arg Trp Val Arg Val Asn
 19525 19530 19535
 Lys Lys Pro Val Tyr Asp Leu Arg Val Lys Ser Thr Gly Leu Arg Glu
 19540 19545 19550
 Gly Cys Glu Tyr Glu Tyr Arg Val Tyr Ala Glu Asn Ala Ala Gly Leu
 19555 19560 19565

Ser Leu Pro Ser Glu Thr Ser Pro Leu Ile Arg Ala Glu Asp Pro Val 1
 19570 19575 19580
 Phe Leu Pro Ser Pro Ser Lys Pro Lys Ile Val Asp Ser Gly Lys
 9585 19590 19595 19600
 Thr Thr Ile Thr Ile Ala Trp Val Lys Pro Leu Phe Asp Gly Gly Ala
 19605 19610 19615
 Pro Ile Thr Gly Tyr Thr Val Glu Tyr Lys Lys Ser Asp Asp Thr Asp
 19620 19625 19630
 Trp Lys Thr Ser Ile Gln Ser Leu Arg Gly Thr Glu Tyr Thr Ile Ser
 19635 19640 19645
 Gly Leu Thr Thr Gly Ala Glu Tyr Val Phe Arg Val Lys Ser Val Asn
 19650 19655 19660 1
 Lys Val Gly Ala Ser Asp Pro Ser Asp Ser Ser Asp Pro Gln Ile Ala
 9665 19670 19675 19680
 Lys Glu Arg Glu Glu Glu Pro Leu Phe Asp Ile Asp Ser Glu Met Arg
 19685 19690 19695
 Lys Thr Leu Ile Val Lys Ala Gly Ala Ser Phe Thr Met Thr Val Pro
 19700 19705 19710
 Phe Arg Gly Arg Pro Val Pro Asn Val Leu Trp Ser Lys Pro Asp Thr
 19715 19720 19725
 Asp Leu Arg Thr Arg Ala Tyr Val Asp Thr Thr Asp Ser Arg Thr Ser 1
 19730 19735 19740
 Leu Thr Ile Glu Asn Ala Asn Arg Asn Asp Ser Gly Lys Tyr Thr Leu
 9745 19750 19755 19760
 Thr Ile Gln Asn Val Leu Ser Ala Ala Ser Leu Thr Leu Val Val Lys
 19765 19770 19775
 Val Leu Asp Thr Pro Gly Pro Pro Thr Asn Ile Thr Val Gln Asp Val
 19780 19785 19790
 Thr Lys Glu Ser Ala Val Leu Ser Trp Asp Val Pro Glu Asn Asp Gly
 19795 19800 19805
 Gly Ala Pro Val Lys Asn Tyr His Ile Glu Lys Arg Glu Ala Ser Lys 1
 19810 19815 19820
 Lys Ala Trp Val Ser Val Thr Asn Asn Cys Asn Arg Leu Ser Tyr Lys
 9825 19830 19835 19840
 Val Thr Asn Leu Gln Glu Gly Ala Ile Tyr Tyr Phe Arg Val Ser Gly
 19845 19850 19855
 Glu Asn Glu Phe Gly Val Gly Ile Pro Ala Glu Thr Lys Glu Gly Val
 19860 19865 19870
 Lys Ile Thr Glu Lys Pro Ser Pro Pro Glu Lys Leu Gly Val Thr Ser
 19875 19880 19885
 Ile Ser Lys Asp Ser Val Ser Leu Thr Trp Leu Lys Pro Glu His Asp 1
 19890 19895 19900
 Gly Gly Ser Arg Ile Val His Tyr Val Val Glu Ala Leu Glu Lys Gly
 9905 19910 19915 19920
 Gln Lys Asn Trp Val Lys Cys Ala Val Ala Lys Ser Thr His His Val
 19925 19930 19935
 Val Ser Gly Leu Arg Glu Asn Ser Glu Tyr Phe Phe Arg Val Phe Ala
 19940 19945 19950
 Glu Asn Gln Ala Gly Leu Ser Asp Pro Arg Glu Leu Leu Leu Pro Val
 19955 19960 19965
 Leu Ile Lys Glu Gln Leu Glu Pro Pro Glu Ile Asp Met Lys Asn Phe 1
 19970 19975 19980
 Pro Ser His Thr Val Tyr Val Arg Ala Gly Ser Asn Leu Lys Val Asp
 9985 19990 19995 20000
 Ile Pro Ile Ser Gly Lys Pro Leu Pro Lys Val Thr Leu Ser Arg Asp
 20005 20010 20015
 Gly Val Pro Leu Lys Ala Thr Met Arg Phe Asn Thr Glu Ile Thr Ala
 20020 20025 20030
 Glu Asn Leu Thr Ile Asn Leu Lys Glu Ser Val Thr Ala Asp Ala Gly
 20035 20040 20045
 Arg Tyr Glu Ile Thr Ala Ala Asn Ser Ser Gly Thr Thr Lys Ala Phe
 20050 20055 20060 2

Ile Asn Ile Val Val Leu Asp Arg Pro Gly Pro Pro Thr Gly Pro Val
 0065 20070 20075 20080
 Val Ile Ser Asp Ile Thr Glu Glu Ser Val Thr Leu Lys Trp Glu Pro
 20085 20090 20095
 Pro Lys Tyr Asp Gly Gly Ser Gln Val Thr Asn Tyr Ile Leu Leu Lys
 20100 20105 20110
 Arg Glu Thr Ser Thr Ala Val Trp Thr Glu Val Ser Ala Thr Val Ala
 20115 20120 20125
 Arg Thr Met Met Lys Val Met Lys Leu Thr Thr Gly Glu Tyr Gln
 20130 20135 20140 2
 Phe Arg Ile Lys Ala Glu Asn Arg Phe Gly Ile Ser Asp His Ile Asp
 0145 20150 20155 20160
 Ser Ala Cys Val Thr Val Lys Leu Pro Tyr Thr Thr Pro Gly Pro Pro
 20165 20170 20175
 Ser Thr Pro Trp Val Thr Asn Val Thr Arg Glu Ser Ile Thr Val Gly
 20180 20185 20190
 Trp His Glu Pro Val Ser Asn Gly Gly Ser Ala Val Val Gly Tyr His
 20195 20200 20205
 Leu Glu Met Lys Asp Arg Asn Ser Ile Leu Trp Gln Lys Ala Asn Lys
 20210 20215 20220 2
 Leu Val Ile Arg Thr Thr His Phe Lys Val Thr Thr Ile Ser Ala Gly
 0225 20230 20235 20240
 Leu Ile Tyr Glu Phe Arg Val Tyr Ala Glu Asn Ala Ala Gly Val Gly
 20245 20250 20255
 Lys Pro Ser His Pro Ser Glu Pro Val Leu Ala Ile Asp Ala Cys Glu
 20260 20265 20270
 Pro Pro Arg Asn Val Arg Ile Thr Asp Ile Ser Lys Asn Ser Val Ser
 20275 20280 20285
 Leu Ser Trp Gln Gln Pro Ala Phe Asp Gly Gly Ser Lys Ile Thr Gly
 20290 20295 20300 2
 Tyr Ile Val Glu Arg Arg Asp Leu Pro Asp Gly Arg Trp Thr Lys Ala
 0305 20310 20315 20320
 Ser Phe Thr Asn Val Thr Glu Thr Gln Phe Thr Ile Ser Gly Leu Thr
 20325 20330 20335
 Gln Asn Ser Gln Tyr Glu Phe Arg Val Phe Ala Arg Asn Ala Val Gly
 20340 20345 20350
 Ser Ile Ser Asn Pro Ser Glu Val Val Gly Pro Ile Thr Cys Ile Asp
 20355 20360 20365
 Ser Tyr Gly Gly Pro Val Ile Asp Leu Pro Leu Glu Tyr Thr Glu Val
 20370 20375 20380 2
 Val Lys Tyr Arg Ala Gly Thr Ser Val Lys Leu Arg Ala Gly Ile Ser
 0385 20390 20395 20400
 Gly Lys Pro Ala Pro Thr Ile Glu Trp Tyr Lys Asp Asp Lys Glu Leu
 20405 20410 20415
 Gln Thr Asn Ala Leu Val Cys Val Glu Asn Thr Thr Asp Leu Ala Ser
 20420 20425 20430
 Ile Leu Ile Lys Asp Ala Asp Arg Leu Asn Ser Gly Cys Tyr Glu Leu
 20435 20440 20445
 Lys Leu Arg Asn Ala Met Ala Ser Ala Ser Ala Thr Ile Arg Val Gln
 20450 20455 20460 2
 Ile Leu Asp Lys Pro Gly Pro Pro Gly Gly Pro Ile Glu Phe Lys Thr
 0465 20470 20475 20480
 Val Thr Ala Glu Lys Ile Thr Leu Leu Trp Arg Pro Pro Ala Asp Asp
 20485 20490 20495
 Gly Gly Ala Lys Ile Thr His Tyr Ile Val Glu Lys Arg Glu Thr Ser
 20500 20505 20510
 Arg Val Val Trp Ser Met Val Ser Glu His Leu Glu Glu Cys Ile Ile
 20515 20520 20525
 Thr Thr Thr Lys Ile Ile Lys Gly Asn Glu Tyr Ile Phe Arg Val Arg
 20530 20535 20540 2
 Ala Val Asn Lys Tyr Gly Ile Gly Glu Pro Leu Glu Ser Asp Ser Val
 0545 20550 20555 20560

Val Ala Lys Asn Ala Phe Val Thr Pro Gly Pro Pro Gly Ile Pro Glu
 20565 20570 20575
 Val Thr Lys Ile Thr Lys Asn Ser Met Thr Val Val Trp Ser Arg Pro
 20580 20585 20590
 Ile Ala Asp Gly Gly Ser Asp Ile Ser Gly Tyr Phe Leu Glu Lys Arg
 20595 20600 20605
 Asp Lys Lys Ser Leu Gly Trp Phe Lys Val Leu Lys Glu Thr Ile Arg
 20610 20615 20620 2
 Asp Thr Arg Gln Lys Val Thr Gly Leu Thr Glu Asn Ser Asp Tyr Gln
 0625 20630 20635 20640
 Tyr Arg Val Cys Ala Val Asn Ala Ala Gly Gln Gly Pro Phe Ser Glu
 20645 20650 20655
 Pro Ser Glu Phe Tyr Lys Ala Ala Asp Pro Ile Asp Pro Pro Gly Pro
 20660 20665 20670
 Pro Ala Lys Ile Arg Ile Ala Asp Ser Thr Lys Ser Ser Ile Thr Leu
 20675 20680 20685
 Gly Trp Ser Lys Pro Val Tyr Asp Gly Gly Ser Ala Val Thr Gly Tyr
 20690 20695 20700 2
 Val Val Glu Ile Arg Gln Gly Glu Glu Glu Glu Trp Thr Thr Val Ser
 0705 20710 20715 20720
 Thr Lys Gly Glu Val Arg Thr Thr Glu Tyr Val Val Ser Asn Leu Lys
 20725 20730 20735
 Pro Gly Val Asn Tyr Tyr Phe Arg Val Ser Ala Val Asn Cys Ala Gly
 20740 20745 20750
 Gln Gly Glu Pro Ile Glu Met Asn Glu Pro Val Gln Ala Lys Asp Ile
 20755 20760 20765
 Leu Glu Ala Pro Glu Ile Asp Leu Asp Val Ala Leu Arg Thr Ser Val
 20770 20775 20780 2
 Ile Ala Lys Ala Gly Glu Asp Val Gln Val Leu Ile Pro Phe Lys Gly
 0785 20790 20795 20800
 Arg Pro Pro Pro Thr Val Thr Trp Arg Lys Asp Glu Lys Asn Leu Gly
 20805 20810 20815
 Ser Asp Ala Arg Tyr Ser Ile Glu Asn Thr Asp Ser Ser Ser Leu Leu
 20820 20825 20830
 Thr Ile Pro Gln Val Thr Arg Asn Asp Thr Gly Lys Tyr Ile Leu Thr
 20835 20840 20845
 Ile Glu Asn Gly Val Gly Glu Pro Lys Ser Ser Thr Val Ser Val Lys
 20850 20855 20860 2
 Val Leu Asp Thr Pro Ala Ala Cys Gln Lys Leu Gln Val Lys His Val
 0865 20870 20875 20880
 Ser Arg Gly Thr Val Thr Leu Leu Trp Asp Pro Pro Leu Ile Asp Gly
 20885 20890 20895
 Gly Ser Pro Ile Ile Asn Tyr Val Ile Glu Lys Arg Asp Ala Thr Lys
 20900 20905 20910
 Arg Thr Trp Ser Val Val Ser His Lys Cys Ser Ser Thr Ser Phe Lys
 20915 20920 20925
 Leu Ile Asp Leu Ser Glu Lys Thr Pro Phe Phe Phe Arg Val Leu Ala
 20930 20935 20940 2
 Glu Asn Glu Ile Gly Ile Gly Glu Pro Cys Glu Thr Thr Glu Pro Val
 0945 20950 20955 20960
 Lys Ala Ala Glu Val Pro Ala Pro Ile Arg Asp Leu Ser Met Lys Asp
 20965 20970 20975
 Ser Thr Lys Thr Ser Val Ile Leu Ser Trp Thr Lys Pro Asp Phe Asp
 20980 20985 20990
 Gly Gly Ser Val Ile Thr Glu Tyr Val Val Glu Arg Lys Gly Lys Gly
 20995 21000 21005
 Glu Gln Thr Trp Ser His Ala Gly Ile Ser Lys Thr Cys Glu Ile Glu
 21010 21015 21020 2
 Val Ser Gln Leu Lys Glu Gln Ser Val Leu Glu Phe Arg Val Phe Ala
 1025 21030 21035 21040
 Lys Asn Glu Lys Gly Leu Ser Asp Pro Val Thr Ile Gly Pro Ile Thr
 21045 21050 21055

Val Lys Glu Leu Ile Ile Thr Pro Glu Val Asp Leu Ser Asp Ile Pro
 21060 21065 21070
 Gly Ala Gln Val Thr Val Arg Ile Gly His Asn Val His Leu Glu Leu
 21075 21080 21085
 Pro Tyr Lys Gly Lys Pro Lys Pro Ser Ile Ser Trp Leu Lys Asp Gly
 21090 21095 21100 2
 Leu Pro Leu Lys Glu Ser Glu Phe Val Arg Phe Ser Lys Thr Glu Asn
 1105 21110 21115 21120
 Lys Ile Thr Leu Ser Ile Lys Asn Ala Lys Lys Glu His Gly Gly Lys
 21125 21130 21135
 Tyr Thr Val Ile Leu Asp Asn Ala Val Cys Arg Ile Ala Val Pro Ile
 21140 21145 21150
 Thr Val Ile Thr Leu Gly Pro Pro Ser Lys Pro Lys Gly Pro Ile Arg
 21155 21160 21165
 Phe Asp Glu Ile Lys Ala Asp Ser Val Ile Leu Ser Trp Asp Val Pro
 21170 21175 21180 2
 Glu Asp Asn Gly Gly Gly Glu Ile Thr Cys Tyr Ser Ile Glu Lys Arg
 1185 21190 21195 21200
 Glu Thr Ser Gln Thr Asn Trp Lys Met Val Cys Ser Ser Val Ala Arg
 21205 21210 21215
 Thr Thr Phe Lys Val Pro Asn Leu Val Lys Asp Ala Glu Tyr Gln Phe
 21220 21225 21230
 Arg Val Arg Ala Glu Asn Arg Tyr Gly Val Ser Gln Pro Leu Val Ser
 21235 21240 21245
 Ser Ile Ile Val Ala Lys His Gln Phe Arg Ile Pro Gly Pro Pro Gly
 21250 21255 21260 2
 Lys Pro Val Ile Tyr Asn Val Thr Ser Asp Gly Met Ser Leu Thr Trp
 1265 21270 21275 21280
 Asp Ala Pro Val Tyr Asp Gly Gly Ser Glu Val Thr Gly Phe His Val
 21285 21290 21295
 Glu Lys Lys Glu Arg Asn Ser Ile Leu Trp Gln Lys Val Asn Thr Ser
 21300 21305 21310
 Pro Ile Ser Gly Arg Glu Tyr Arg Ala Thr Gly Leu Val Glu Gly Leu
 21315 21320 21325
 Asp Tyr Gln Phe Arg Val Tyr Ala Glu Asn Ser Ala Gly Leu Ser Ser
 21330 21335 21340 2
 Pro Ser Asp Pro Ser Lys Phe Thr Leu Ala Val Ser Pro Val Asp Pro
 1345 21350 21355 21360
 Pro Gly Thr Pro Asp Tyr Ile Asp Val Thr Arg Glu Thr Ile Thr Leu
 21365 21370 21375
 Lys Trp Asn Pro Pro Leu Arg Asp Gly Gly Ser Lys Ile Val Gly Tyr
 21380 21385 21390
 Ser Ile Glu Lys Arg Gln Gly Asn Glu Arg Trp Val Arg Cys Asn Phe
 21395 21400 21405
 Thr Asp Val Ser Glu Cys Gln Tyr Thr Val Thr Gly Leu Ser Pro Gly
 21410 21415 21420 2
 Asp Arg Tyr Glu Phe Arg Ile Ile Ala Arg Asn Ala Val Gly Thr Ile
 1425 21430 21435 21440
 Ser Pro Pro Ser Gln Ser Ser Gly Ile Ile Met Thr Arg Asp Glu Asn
 21445 21450 21455
 Val Pro Pro Ile Val Glu Phe Gly Pro Glu Tyr Phe Asp Gly Leu Ile
 21460 21465 21470
 Ile Lys Ser Gly Glu Ser Leu Arg Ile Lys Ala Leu Val Gln Gly Arg
 21475 21480 21485
 Pro Val Pro Arg Val Thr Trp Phe Lys Asp Gly Val Glu Ile Glu Lys
 21490 21495 21500 2
 Arg Met Asn Met Glu Ile Thr Asn Val Leu Gly Ser Thr Ser Leu Phe
 1505 21510 21515 21520
 Val Arg Asp Ala Thr Arg Asp His Arg Gly Val Tyr Thr Val Glu Ala
 21525 21530 21535
 Lys Asn Ala Ser Gly Ser Ala Lys Ala Glu Ile Lys Val Lys Val Gln
 21540 21545 21550

Asp Thr Pro Gly Lys Val Val Gly Pro Ile Arg Phe Thr Asn Ile Thr
 21555 21560 21565
 Gly Glu Lys Met Thr Leu Trp Trp Asp Ala Pro Leu Asn Asp Gly Cys
 21570 21575 21580 2
 Ala Pro Ile Thr His Tyr Ile Ile Glu Lys Arg Glu Thr Ser Arg Leu
 1585 21590 21595 21600
 Ala Trp Ala Leu Ile Glu Asp Lys Cys Glu Ala Gln Ser Tyr Thr Ala
 21605 21610 21615
 Ile Lys Leu Ile Asn Gly Asn Glu Tyr Gln Phe Arg Val Ser Ala Val
 21620 21625 21630
 Asn Lys Phe Gly Val Gly Arg Pro Leu Asp Ser Asp Pro Val Val Ala
 21635 21640 21645
 Gln Ile Gln Tyr Thr Val Pro Asp Ala Pro Gly Ile Pro Glu Pro Ser
 21650 21655 21660 2
 Asn Ile Thr Gly Asn Ser Ile Thr Leu Thr Trp Ala Arg Pro Glu Ser
 1665 21670 21675 21680
 Asp Gly Gly Ser Glu Ile Gln Gln Tyr Ile Leu Glu Arg Arg Glu Lys
 21685 21690 21695
 Lys Ser Thr Arg Trp Val Lys Val Ile Ser Lys Arg Pro Ile Ser Glu
 21700 21705 21710
 Thr Arg Phe Lys Val Thr Gly Leu Thr Glu Gly Asn Glu Tyr Glu Phe
 21715 21720 21725
 His Val Met Ala Glu Asn Ala Ala Gly Val Gly Pro Ala Ser Gly Ile
 21730 21735 21740 2
 Ser Arg Leu Ile Lys Cys Arg Glu Pro Val Asn Pro Pro Gly Pro Pro
 1745 21750 21755 21760
 Thr Val Val Lys Val Thr Asp Thr Ser Lys Thr Thr Val Ser Leu Glu
 21765 21770 21775
 Trp Ser Lys Pro Val Phe Asp Gly Gly Met Glu Ile Ile Gly Tyr Ile
 21780 21785 21790
 Ile Glu Met Cys Lys Thr Asp Leu Gly Asp Trp His Lys Val Asn Ala
 21795 21800 21805
 Glu Ala Cys Val Lys Thr Arg Tyr Thr Val Thr Asp Leu Gln Ala Gly
 21810 21815 21820 2
 Glu Glu Tyr Lys Phe Arg Val Ser Ala Ile Asn Gly Ala Gly Lys Gly
 1825 21830 21835 21840
 Asp Ser Cys Glu Val Thr Gly Thr Ile Lys Ala Val Asp Arg Leu Thr
 21845 21850 21855
 Ala Pro Glu Leu Asp Ile Asp Ala Asn Phe Lys Gln Thr His Val Val
 21860 21865 21870
 Arg Ala Gly Ala Ser Ile Arg Leu Phe Ile Ala Tyr Gln Gly Arg Pro
 21875 21880 21885
 Thr Pro Thr Ala Val Trp Ser Lys Pro Asp Ser Asn Leu Ser Leu Arg
 21890 21895 21900 2
 Ala Asp Ile His Thr Thr Asp Ser Phe Ser Thr Leu Thr Val Glu Asn
 1905 21910 21915 21920
 Cys Asn Arg Asn Asp Ala Gly Lys Tyr Thr Leu Thr Val Glu Asn Asn
 21925 21930 21935
 Ser Gly Ser Lys Ser Ile Thr Phe Thr Val Lys Val Leu Asp Thr Pro
 21940 21945 21950
 Gly Pro Pro Gly Pro Ile Thr Phe Lys Asp Val Thr Arg Gly Ser Ala
 21955 21960 21965
 Thr Leu Met Trp Asp Ala Pro Leu Leu Asp Gly Gly Ala Arg Ile His
 21970 21975 21980 2
 His Tyr Val Val Glu Lys Arg Glu Ala Ser Arg Arg Ser Trp Gln Val
 1985 21990 21995 22000
 Ile Ser Glu Lys Cys Thr Arg Gln Ile Phe Lys Val Asn Asp Leu Ala
 22005 22010 22015
 Glu Gly Val Pro Tyr Tyr Phe Arg Val Ser Ala Val Asn Glu Tyr Gly
 22020 22025 22030
 Val Gly Glu Pro Tyr Glu Met Pro Glu Pro Ile Val Ala Thr Glu Gln
 22035 22040 22045

Pro Ala Pro Pro Arg Arg Leu Asp Val Val Asp Thr Ser Lys Ser Ser 2
 22050 22055 22060
 Ala Val Leu Ala Trp Leu Lys Pro Asp His Asp Gly Gly Ser Arg Ile
 2065 22070 22075 22080
 Thr Gly Tyr Leu Leu Glu Met Arg Gln Lys Gly Ser Asp Leu Trp Val
 22085 22090 22095
 Glu Ala Gly His Thr Lys Gln Leu Thr Phe Thr Val Glu Arg Leu Val
 22100 22105 22110
 Glu Lys Thr Glu Tyr Glu Phe Arg Val Lys Ala Lys Asn Asp Ala Gly
 22115 22120 22125
 Tyr Ser Glu Pro Arg Glu Ala Phe Ser Ser Val Ile Ile Lys Glu Pro
 22130 22135 22140 2
 Gln Ile Glu Pro Thr Ala Asp Leu Thr Gly Ile Thr Asn Gln Leu Ile
 2145 22150 22155 22160
 Thr Cys Lys Ala Gly Ser Pro Phe Thr Ile Asp Val Pro Ile Ser Gly
 22165 22170 22175
 Arg Pro Ala Pro Lys Val Thr Trp Lys Leu Glu Glu Met Arg Leu Lys
 22180 22185 22190
 Glu Thr Asp Arg Val Ser Ile Thr Thr Thr Lys Asp Arg Thr Thr Leu
 22195 22200 22205
 Thr Val Lys Asp Ser Met Arg Gly Asp Ser Gly Arg Tyr Phe Leu Thr 2
 22210 22215 22220
 Leu Glu Asn Thr Ala Gly Val Lys Thr Phe Ser Val Thr Val Val Val
 2225 22230 22235 22240
 Ile Gly Arg Pro Gly Pro Val Thr Gly Pro Ile Glu Val Ser Ser Val
 22245 22250 22255
 Ser Ala Glu Ser Cys Val Leu Ser Trp Gly Glu Pro Lys Asp Gly Gly
 22260 22265 22270
 Gly Thr Glu Ile Thr Asn Tyr Ile Val Glu Lys Arg Glu Ser Gly Thr
 22275 22280 22285
 Thr Ala Trp Gln Leu Val Asn Ser Ser Val Lys Arg Thr Gln Ile Lys
 22290 22295 2300 2
 Val Thr His Leu Thr Lys Tyr Met Glu Tyr Ser Phe Arg Val Ser Ser
 2305 22310 22315 22320
 Glu Asn Arg Phe Gly Val Ser Lys Pro Leu Glu Ser Ala Pro Ile Ile
 22325 22330 22335
 Ala Glu His Pro Phe Val Pro Pro Ser Ala Pro Thr Arg Pro Glu Val
 22340 22345 22350
 Tyr His Val Ser Ala Asn Ala Met Ser Ile Arg Trp Glu Glu Pro Tyr
 22355 22360 22365
 His Asp Gly Gly Ser Lys Ile Ile Gly Tyr Trp Val Glu Lys Lys Glu 2
 22370 22375 22380
 Arg Asn Thr Ile Leu Trp Val Lys Glu Asn Lys Val Pro Cys Leu Glu
 2385 22390 22395 22400
 Cys Asn Tyr Lys Val Thr Gly Leu Val Glu Gly Leu Glu Tyr Gln Phe
 22405 22410 22415
 Arg Thr Tyr Ala Leu Asn Ala Ala Gly Val Ser Lys Ala Ser Glu Ala
 22420 22425 22430
 Ser Arg Pro Ile Met Ala Gln Asn Pro Val Asp Ala Pro Gly Arg Pro
 22435 22440 22445
 Glu Val Thr Asp Val Thr Arg Ser Thr Val Ser Leu Ile Trp Ser Ala 2
 22450 22455 22460
 Pro Ala Tyr Asp Gly Gly Ser Lys Val Val Gly Tyr Ile Ile Glu Arg
 2465 22470 22475 22480
 Lys Pro Val Ser Glu Val Gly Asp Gly Arg Trp Leu Lys Cys Asn Tyr
 22485 22490 22495
 Thr Ile Val Ser Asp Asn Phe Phe Thr Val Thr Ala Leu Ser Glu Gly
 22500 22505 22510
 Asp Thr Tyr Glu Phe Arg Val Leu Ala Lys Asn Ala Ala Gly Val Ile
 22515 22520 22525
 Ser Lys Gly Ser Glu Ser Thr Gly Pro Val Thr Cys Arg Asp Glu Tyr 2
 22530 22535 22540

Ala Pro Pro Lys Ala Glu Leu Asp Ala Arg Leu His Gly Asp Leu Val
 2545 22550 22555 22560
 Thr Ile Arg Ala Gly Ser Asp Leu Val Leu Asp Ala Ala Val Gly Gly
 22565 22570 22575
 Lys Pro Glu Pro Lys Ile Ile Trp Thr Lys Gly Asp Lys Glu Leu Asp
 22580 22585 22590
 Leu Cys Glu Lys Val Ser Leu Gln Tyr Thr Gly Lys Arg Ala Thr Ala
 22595 22600 22605
 Val Ile Lys Phe Cys Asp Arg Ser Asp Ser Gly Lys Tyr Thr Leu Thr
 22610 22615 22620 2
 Val Lys Asn Ala Ser Gly Thr Lys Ala Val Ser Val Met Val Lys Val
 2625 22630 22635 22640
 Leu Asp Ser Pro Gly Pro Cys Gly Lys Leu Thr Val Ser Arg Val Thr
 22645 22650 22655
 Gln Glu Lys Cys Thr Leu Ala Trp Ser Leu Pro Gln Glu Asp Gly Gly
 22660 22665 22670
 Ala Glu Ile Thr His Tyr Ile Val Glu Arg Arg Glu Thr Ser Arg Leu
 22675 22680 22685
 Asn Trp Val Ile Val Glu Gly Glu Cys Pro Thr Leu Ser Tyr Val Val
 22690 22695 22700 2
 Thr Arg Leu Ile Lys Asn Asn Glu Tyr Ile Phe Arg Val Arg Ala Val
 2705 22710 22715 22720
 Asn Lys Tyr Gly Pro Gly Val Pro Val Glu Ser Glu Pro Ile Val Ala
 22725 22730 22735
 Arg Asn Ser Phe Thr Ile Pro Ser Pro Pro Gly Ile Pro Glu Glu Val
 22740 22745 22750
 Gly Thr Gly Lys Glu His Ile Ile Ile Gln Trp Thr Lys Pro Glu Ser
 22755 22760 22765
 Asp Gly Gly Asn Glu Ile Ser Asn Tyr Leu Val Asp Lys Arg Glu Lys
 22770 22775 22780 2
 Glu Ser Leu Arg Trp Thr Arg Val Asn Lys Asp Tyr Val Val Tyr Asp
 2785 22790 22795 22800
 Thr Arg Leu Lys Val Thr Ser Leu Met Glu Gly Cys Asp Tyr Gln Phe
 22805 22810 22815
 Arg Val Thr Ala Val Asn Ala Ala Gly Asn Ser Glu Pro Ser Glu Arg
 22820 22825 22830
 Ser Asn Phe Ile Ser Cys Arg Glu Pro Ser Tyr Thr Pro Gly Pro Pro
 22835 22840 22845
 Ser Ala Pro Arg Val Val Asp Thr Thr Lys His Ser Ile Ser Leu Ala
 22850 22855 22860 2
 Trp Thr Lys Pro Met Tyr Asp Gly Gly Thr Asp Ile Val Gly Tyr Val
 2865 22870 22875 22880
 Leu Glu Met Gln Glu Lys Asp Thr Asp Gln Trp Tyr Arg Val His Thr
 22885 22890 22895
 Asn Ala Thr Ile Arg Asn Thr Glu Phe Thr Val Pro Asp Leu Lys Met
 22900 22905 22910
 Gly Gln Lys Tyr Ser Phe Arg Val Ala Ala Val Asn Val Lys Gly Met
 22915 22920 22925
 Ser Glu Tyr Ser Glu Ser Ile Ala Glu Ile Glu Pro Val Glu Arg Ile
 22930 22935 22940 2
 Glu Ile Pro Asp Leu Glu Leu Ala Asp Asp Leu Lys Lys Thr Val Thr
 2945 22950 22955 22960
 Ile Arg Ala Gly Ala Ser Leu Arg Leu Met Val Ser Val Ser Gly Arg
 22965 22970 22975
 Pro Pro Pro Val Ile Thr Trp Ser Lys Gln Gly Ile Asp Leu Ala Ser
 22980 22985 22990
 Arg Ala Ile Ile Asp Thr Thr Glu Ser Tyr Ser Leu Leu Ile Val Asp
 22995 23000 23005
 Lys Val Asn Arg Tyr Asp Ala Gly Lys Tyr Thr Ile Glu Ala Glu Asn
 23010 23015 23020 2
 Gln Ser Gly Lys Lys Ser Ala Thr Val Leu Val Lys Val Tyr Asp Thr
 3025 23030 23035 23040

Pro	Gly	Pro	Cys	Pro	Ser	Val	Lys	Val	Lys	Glu	Val	Ser	Arg	Asp	Ser
Val	Thr	Ile	Thr	Trp	Glu	Ile	Pro	Thr	Ile	Asp	Gly	Gly	Ala	Pro	Ile
Asn	Asn	Tyr	Ile	Val	Glu	Lys	Arg	Glu	Ala	Ala	Met	Arg	Ala	Phe	Lys
Thr	Val	Thr	Thr	Lys	Cys	Ser	Lys	Thr	Leu	Tyr	Arg	Ile	Ser	Gly	Leu
Val	Glu	Gly	Thr	Met	His	Tyr	Phe	Arg	Val	Leu	Pro	Glu	Asn	Ile	Tyr
Gly	Ile	Gly	Glu	Pro	Cys	Glu	Thr	Ser	Asp	Ala	Val	Leu	Val	Ser	Glu
Val	Pro	Leu	Val	Pro	Ala	Lys	Leu	Glu	Val	Val	Asp	Val	Thr	Lys	Ser
Thr	Val	Thr	Leu	Ala	Trp	Glu	Lys	Pro	Leu	Tyr	Asp	Gly	Gly	Ser	Arg
Leu	Thr	Gly	Tyr	Val	Leu	Glu	Ala	Cys	Lys	Ala	Gly	Thr	Glu	Arg	Trp
Met	Lys	Val	Val	Thr	Leu	Lys	Pro	Thr	Val	Leu	Glu	His	Thr	Val	Thr
Ser	Leu	Asn	Glu	Gly	Glu	Gln	Tyr	Leu	Phe	Arg	Ile	Arg	Ala	Gln	Asn
Glu	Lys	Gly	Val	Ser	Glu	Pro	Arg	Glu	Thr	Val	Thr	Ala	Val	Thr	Val
Gln	Asp	Leu	Arg	Val	Leu	Pro	Thr	Ile	Asp	Leu	Ser	Thr	Met	Pro	Gln
Lys	Thr	Ile	His	Val	Pro	Ala	Gly	Arg	Pro	Val	Glu	Leu	Val	Ile	Pro
Ile	Ala	Gly	Arg	Pro	Pro	Pro	Ala	Ala	Ser	Trp	Phe	Phe	Ala	Gly	Ser
Lys	Leu	Arg	Glu	Ser	Glu	Arg	Val	Thr	Val	Glu	Thr	His	Thr	Lys	Val
Ala	Lys	Leu	Thr	Ile	Arg	Glu	Thr	Thr	Ile	Arg	Asp	Thr	Gly	Glu	Tyr
Thr	Leu	Glu	Leu	Lys	Asn	Val	Thr	Gly	Thr	Thr	Ser	Glu	Thr	Ile	Lys
Val	Ile	Ile	Leu	Asp	Lys	Pro	Gly	Pro	Pro	Thr	Gly	Pro	Ile	Lys	Ile
Asp	Glu	Ile	Asp	Ala	Thr	Ser	Ile	Thr	Ile	Ser	Trp	Glu	Pro	Pro	Glu
Leu	Asp	Gly	Gly	Ala	Pro	Leu	Ser	Gly	Tyr	Val	Val	Glu	Gln	Arg	Asp
Ala	His	Arg	Pro	Gly	Trp	Leu	Pro	Val	Ser	Glu	Ser	Val	Thr	Arg	Ser
Thr	Phe	Lys	Phe	Thr	Arg	Leu	Thr	Glu	Gly	Asn	Glu	Tyr	Val	Phe	Arg
Val	Ala	Ala	Thr	Asn	Arg	Phe	Gly	Ile	Gly	Ser	Tyr	Leu	Gln	Ser	Glu
Val	Ile	Glu	Cys	Arg	Ser	Ile	Arg	Ile	Pro	Gly	Pro	Pro	Glu	Thr	Tyr
Leu	Gln	Ile	Phe	Asp	Val	Ser	Arg	Asp	Gly	Met	Thr	Leu	Thr	Trp	Tyr
Pro	Pro	Glu	Asp	Asp	Gly	Gly	Ser	Gln	Val	Thr	Gly	Tyr	Ile	Val	Glu
Arg	Lys	Glu	Val	Arg	Ala	Asp	Arg	Trp	Val	Arg	Val	Asn	Lys	Val	Pro
Val	Thr	Met	Thr	Arg	Tyr	Arg	Ser	Thr	Gly	Leu	Thr	Glu	Gly	Leu	Glu
Tyr	Glu	His	Arg	Val	Thr	Ala	Ile	Asn	Ala	Arg	Gly	Ser	Gly	Lys	Pro
Ser	Arg	Pro	Ser	Lys	Pro	Ile	Val	Ala	Met	Asp	Pro	Ile	Ala	Pro	Pro

Gly Lys Pro Gln Asn Pro Arg Val Thr Asp Thr Thr Arg Thr Ser Val
 23540 23545 23550
 Ser Leu Ala Trp Ser Val Pro Glu Asp Glu Gly Gly Ser Lys Val Thr
 23555 23560 23565
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22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/01212

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; A61K 48/00; C12N 15/00

US CL : 435/6; 514/44; 800/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6; 514/44; 800/21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, caplus, medline, uspatful

search terms: titin gene, mutation, pickwick, heart disease, cardiac, cardio?, zebrafish

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -----	SATOH. M. Structural Analysis of the Titin Gene in Hypertrophic Cardiomyopathy: Identification of a Novel Disease Gene. Biochemical and Biophysical Research Communications. August 1999. Vol 262. pages 411-417, especially abstract, page 412, Fig.3, page 414.	1-6 -----
A		7-19
A	SIU. B.L. Familial Dilated Cardiomyopathy Locus Maps to Chromosome 2q31. Circulation. 02 March 1999. Vol 99. pages 1022-1026, especially abstract, Fig. 3.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* I* Inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
* A* document defining the general state of the art which is not considered to be of particular relevance	* N* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* B* earlier document published on or after the international filing date	* Y* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* &* document member of the same patent family
* O* document referring to an oral disclosure, use, exhibition or other means	
* P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 FEBRUARY 2001

Date of mailing of the international search report

16 MAY 2001

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